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T H E S I S

for the Degree of M.D., Edinburgh University.

on

STRUCTURE of UTERINE MUCOSA and its BEARING

on CHANGES in MENSTRUATION and PREGNANCY.

Mode of action of foetal structures and opening-up of
maternal vessels. Imbedding of human ovum with ac-
count of very early specimen. Function of the
decidua.

by

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I N D E X.

VOL. I.

INTRODUCTION.

PAGE.

SECTION I.	Structure of Uterine Mucous membrane	1.
	Blood vessels.	25.
	Elastic Tissue in Endometrium	33.
	Network of Stroma	53.
SECTION II.	MENSTRUATION.	
	Investigations into mucosa changes during menstruation.	88.
	Surface Epithelium and Glands.	94.
	Blood vessels and Stroma.	98.
	Cause of the Blood Escape.	115.
	Rôle of the Intimal Cells.	128.
	Rôle of Stroma Protoplasm.	132.
	Structure of Tissue Network of Stroma and true interpretation of Inter-cellular spaces.	146.
SECTION III.	MODE OF ACTION OF CHORIONIC STRUCTURES.	
	Pregnant Tube.	161.
	Causation of Oedema.	181.
	Significance of Endothelial changes.	211.
	Connective tissue cells.	216.
	Cause of Blood escape.	244.
	Significance of direct Infiltration of vessel walls.	250.
	Mode/	

	PAGE.
Mode of Formation of Sinuses	257.
" " " " New vessels	264.
<u>SECTION IV.</u> ACTION OF CHORIONIC CELLS ON THE	
MATERNAL TISSUES AS SEEN IN RE-	
TENTION OF PLACENTAL FRAGMENTS	272.
<u>SECTION V.</u> THE MODE OF ACTION OF THE CHORI-	
ONIC EPITHELIUM ON THE MATERNAL	
TISSUES AS STUDIED IN CHORION-	
EPITHELIOMA	283.
Cause of the blood escape from	
maternal vessels	294.
Mode of Formation of Sinuses	321.
New vessel Formation	325.
Is a direct infiltration of the	
vessel walls the cause of the	
Blood escape?	326.
<u>SECTION VI.</u> CAUSATION OF OEDEMA	348.
<u>SECTION VII.</u> NATURE OF CHORIONIC INFLUENCE	
AND MODE OF ITS SPREAD	357.
<u>SECTION VIII.</u> CHANGES IN UTERUS IN NORMAL	
PREGNANCY	363.
Formation of ovum bed and opening-	
up of Maternal vessels	368.
Changes in vessel walls and cells	
of decidua	400.
Changes in vessels in muscular	
wall of Pregnant Uterus	404.
Mode/	

Mode of fluid absorption by chorionic surface	409.
--	------

SECTION IX. DECIDUAL FORMATION AND FUNCTION

OF DECIDUAL MEMBRANE	415.
----------------------	------

Decidual changes in Pregnant Tube	415.
--------------------------------------	------

Decidual changes in Uterus in Placental fragments	427.
--	------

Decidual changes in Chorion- epithelioma	429.
---	------

Decidual membrane of Normal Pregnancy	433.
--	------

SECTION X. ADDENDUM.

Preliminary account of very early Human Ovum	472.
---	------

Account of second early Ovum (lent by Dr Teacher)	489.
--	------

BIBLIOGRAPHY

VOLUME II

Illustrations

I N T R O D U C T I O N .

The following thesis embodies the results of investigations conducted over a period of about one year and a half. A great part of the work was carried out in the Royal College of Physicians Laboratory, Edinburgh.

The investigations originated in the discovery of a distinct resemblance between the modes of production of the oedematous and haemorrhagic infiltration of the tissues in the menstruating uterine mucosa and in the wall of the pregnant Fallopian Tube. This discovery led, on the one hand, to a study of the structure of the uterine mucous membrane, and, on the other hand, to an extension of the investigations on the mode of action of the foetal elements. By this means I hoped to arrive at an explanation of the menstrual changes and of the alterations which the mucosa exhibits during pregnancy. That this hope has been realised I shall endeavour to prove in the course of the thesis.

The latter portion of the research, namely the investigation into the maternal tissue changes induced by the foetal elements, has been carried out largely on the pregnant tube, on the uterus in the cases/

Berry Hart.

The coloured plates were drawn for me by Mr Richard Muir, to whom I am grateful for the great trouble he has taken in their preparation. The microphotographs were taken in the Laboratory of the Royal College of Physicians.

The collection of microscopic slides which I am sending in with the thesis comprises typical examples of the specimens on which the investigations were conducted. The remainder of the sections may be consulted in the Midwifery Department of the University. I may state that I shall be glad at any time to give a personal demonstration of my slides.

The mucous membrane lining the uterine body in the resting state is of a pinkish-red color; it is composed of a simple columnar epithelium, the cells of which are tall and narrow, with a large, oval, centrally placed nucleus, and a small, clear, vacuole at the base. The surface is smooth and glistening.

SECTION I.

STRUCTURE of the UTERINE MUCOUS MEMBRANE.

The mucous membrane of the uterus is composed of a simple columnar epithelium, the cells of which are tall and narrow, with a large, oval, centrally placed nucleus, and a small, clear, vacuole at the base. The surface is smooth and glistening. The thickness of the mucous membrane varies from 1 to 2 mm. The mucous membrane is highly vascular, and is supplied with a rich network of blood vessels. The uterine glands are situated in the submucosa, and are composed of a simple columnar epithelium, the cells of which are tall and narrow, with a large, oval, centrally placed nucleus, and a small, clear, vacuole at the base. The glands are highly vascular, and are supplied with a rich network of blood vessels. The uterine glands are highly coiled, and their ducts open into the uterine cavity. The uterine glands are highly sensitive to the influence of the female sex hormones, and their activity is increased during the menstrual cycle. The uterine glands are highly sensitive to the influence of the female sex hormones, and their activity is increased during the menstrual cycle.

THE SURFACE EPITHELIUM.

The columnar cells forming this layer have a distinct ciliated margin. They are, for the most part, closely packed together, though here and there they may be separated by spaces in which small cells are present. The nuclei are usually oval in shape and are situated towards the base of the cells. Under some circumstances they become more rounded and they rise up towards the centre of the cell-body. Where the epithelium is lifted up in any condition, and this applies, also, to the cells forming the glands, it is often seen that the bases of the cells are connected with the stroma elements by means of protoplasmic filaments.

THE GLANDS.

These are of the tubular variety, and are, for the most part, unbranched. In some places, especially towards their deeper parts, they may divide into two, or, more rarely, three branches. They usually run somewhat obliquely to the surface, and, in the ordinary resting stage of the mucosa, they pursue a course which is fairly straight. In some conditions, e.g. menstruation, and in pathological states, /

states, they present a tortuous or cork-screw like appearance. This is sometimes exhibited to a very marked degree.

The glandular epithelium resembles that covering the surface of the mucosa, consisting, namely, of columnar ciliated cells. The gland lumen is round on transverse section, and oval on oblique section.

The glands can, for the most part, be traced in serial sections throughout the entire thickness of the mucosa, right to the muscular coat. Here they sometimes commence in slightly bulbous expansions. In some places they are seen to burrow into the muscle, sometimes, even under normal circumstances, for a considerable distance. They are seen to be imbedded in the portions of the stroma, which project between the superficial muscle bundles.

With regard to the presence or absence of a specialised basement membrane immediately under the epithelial cells of the surface and of the glands and comparable to similar structures found elsewhere there is still a difference of opinion in the literature. This subject will be approached in a later part of this investigation; suffice it for the present to state that, in some parts of the mucosa,
a /

a layer of flattened cells may be seen under the bases of the columnar cells, which apparently differ from the adjacent stroma cell.

THE INTERGLANDULAR STROMA.

This, as has already been stated, comprises the main mass of the mucous membrane of the uterus. The structural features of this tissue, with which this investigation is especially concerned, has been described in widely different ways by different observers, and round it a large amount of literature has grown within recent years. The wide divergence of opinion, which becomes apparent even after a cursory glance through the literature, would seem to be dependent, to a large extent, on the many and varying appearances, which the uterine mucosa exhibits. So great are the differences within normal limits, that two perfectly healthy specimens from the same uterus may present histological characters so widely divergent, as almost, at first sight, to justify the opinion that they have been derived from entirely different sources. This fact will be borne out in the course of this record. We are thus provided with a clue to the explanation of the many and conflicting results obtained.

Under the microscope the interglandular stroma of the mucosa is seen to consist, under ordinary circumstances, of nuclei densely packed together, each surrounded by a layer of protoplasm of varying thickness. The cells are seen to be separated from one another by clear intercellular spaces of varying size. Bridging across these spaces the adjacent cells are connected with one another by protoplasmic filaments. In most specimens, more marked in some than in others, a fine tissue network is seen between the cells. Coursing through the stroma arterioles are seen; they consist of the continuations of the ovarian and uterine arteries situated in the muscular coat, and pursue a spiral course throughout the stroma. They, for the most part, pass right to the surface, giving off small branches en route; here they break up into a fine capillary plexus, from which the blood is carried back to the muscular coat by means of veins with more poorly supported walls.

Before directing attention to the investigations to be recorded, which were carried out with the purpose of throwing further light on the structure of the uterine stroma and more especially of the blood-vessels, and, if possible, of harmonizing the opposing /

opposing views, it will be necessary to refer, somewhat in brief, to the most important papers previously written.

The difficulty of a correct structural interpretation of the apparently simple tissue just described has given rise to endless controversy.

(1)

HENLE stated that the stroma is formed by thickly-packed nuclei and cells, which sometimes grow into short rhombic plates. The spaces between the cells are filled with a finely granular material. On

being teased out the cells are removed and a fine

(2)

network is left behind. FREI maintained that it is composed of star and spindle-shaped cells, which form a fine network; in this way it resembles the

(3)

structure of a lymphatic organ. KRAUSE considered it to be formed by spindle cells with long oval nuclei, and of rounded cells, which are connected with one another by processes in such a way as to

(4)

produce a fine network. KÖLLIKER believed it to be formed of spindle cells arranged singly or in bundles. In addition single round cells and a few

free nuclei are present, all imbedded in an amorphous

(5)

substance. KUNDRAT and ENGELMANN looked on the stroma as consisting of spindle and round cells

lying in an amorphous intervening material. There is present, also, a fine network of threads, thicker in the deeper portions than at the surface.

ROBIN/

(6)

ROBIN considered the stroma as composed of embryonic ovoid, granular cells, separated by a finely granular amorphous material. In addition spindle cells and connective tissue fibres are present.

One of the most important contributions to the literature was a paper published in 1874 by ⁽⁷⁾ Leopold. As it will be necessary to refer frequently to the work of this observer, I shall consider his investigations in somewhat greater detail. According to him the interglandular stroma of the uterine mucosa consists of two distinct and separate entities, a connective tissue network, and a large number of flattened cells, (Zellplättchen or plättchenförmigen Zellen,) The connective tissue, which is continuous with the connective tissue between the bundles of the muscular wall, forms a scaffold or framework on which the stroma is built. When the surface of the muscle is reached the connective tissue bundles become separated into two different parts: the outer clothes the inner limit of the muscle and thereby separates it from the mucosa, whilst the inner passes between the glands and vessels as a fine network. These innermost connective tissue fibres become less and less evident as the surface is reached. The spaces of the network /

network are lined throughout by the cell-plates and form a vast intercommunicating system filled with lymph. By experiment Leopold was enabled to inject this system from the subserous and intermuscular lymphatics and he therefore concluded that the stroma is to be considered as an extensive lymphatic sponge, the cell-plates corresponding to the endothelial cells of a lymphatic vessel. In animals, (such as the pig, etc, in which his experiments were carried out) the spaces are larger and the cells are more widely separated than in the human uterus, to which, however, the same description applies.

The glands and blood-vessels run straight through this lymph-system, separated from the latter only by a layer of the connective tissue, and the cell-plates. These form the so-called basement membrane, and, massed round the endothelium and the blood-vessels in varying numbers, they produce the differing thickness of the vessel walls.

The arteries pursue a winding course from the muscle wall of the uterus to the surface and there (often under the epithelium,) they form a capillary network, from which the veins, situated mostly in the proximity of the arteries, carry the blood back /

back to the muscle. Arterial twigs are often seen surrounding the glands.

According to Leopold the finely granular material present in the intercellular space is coagulated lymph.

⁽⁸⁾
CHAMPIONNIÈRE in a work published in the year after that in which Leopold's investigations appeared, considers the mucosa, like this author, as forming a lymphatic surface.

⁽⁹⁾
According to MÖRICKE, (in a work which will be subsequently referred to in connection with the process of menstruation,) the interglandular stroma is formed by round and spindle cells, some free nuclei and an intervening finely granular amorphous material. The round cells are distinctly granular. The other cells are oval, or spindle-shaped, with a clear, glistening nucleus, which fills almost the whole cell and only leaves a small amount of protoplasm at either pole. These cells are connected by means of long, fine filaments of protoplasm, which are often torn across. The free nuclei are oval; near them portions of protoplasm, resembling that found in the spindle cells, are seen. The nuclei, then, probably correspond to spindle cells which have lost their protoplasm. The connective tissue is arranged in the form of a fine network, in /

in the meshes of which the round cells and a finely granular substance are present.

(10)

FOIRIER, like Leopold, looks on the uterine stroma as a lymphatic surface. MINOT in his

(11)

"Human Embryology" describes the uterine stroma as consisting of an indifferentiated embryonic tissue.

(12)

NAGEL returns to the conception, previously noted under the name of FREI, that the stroma consists of

(13)

a lymphatic tissue. JOHNSTONE looks on it as an

(14)

adenoid tissue. WILLIAMS agrees with MINOT in considering the stroma as consisting of an embryonic

tissue and he moreover declares that "when prepar-

ations from the endometrium are treated by appropriate

methods, an abundant reticulum can be demonstrated

throughout its entire extent, which forms the scaffolding upon which it is constructed." He describes

the arteries as pursuing a spiral course through the stroma, and breaking into a capillary network just

(15)

beneath the surface epithelium. WEBSTER, also,

looks on the intergland stroma as a tissue of low or embryonic type. "It is best described," he says,

"as mainly consisting of delicate anastomosing nucleated masses of protoplasm."

This brief summary of the literature is sufficient to indicate the very varying and conflicting /

conflicting ideas entertained by different observers as to the structure of the stroma of the uterine mucosa. The main difference of opinion centres round the exact histological relationship between the cells of the stroma and the intervening branching and interlacing fibrils, which form the network so frequently referred to. About the finely granular, amorphous material or Zwischensubstanz, there is less divergence of opinion; the larger number of observers agree with Leopold in considering it as coagulated lymph in the intercellular spaces. According to this same author the fibrillar network constitutes a separate and independent histological entity and forms a sort of scaffold on which the stroma is constructed. The cells are flattened like endothelium and line the intercommunicating spaces of the connective tissue network, in this way forming a complex lymphatic surface or sponge. This belief is endorsed by many of the older writers; to-day it seems to commend itself to only a few observers, though WILLIAMS would seem to believe in the existence of this network as a distinct and independent entity. Most of the workers in the subject lean towards the idea that the network is merely formed by the branching protoplasmic processes /

processes of the stroma cells. A fact which has struck me somewhat forcibly in the study of the literature on the subject is the meagre attention which has been given to the structure of the blood-vessels of the mucosa. This is all the more surprising in view of the fact that the structural changes which the stroma exhibits during menstruation and pregnancy are, at any rate, in the initial stages entirely dependent on vascular alterations.

MATERIAL. In conducting the following investigations I have employed almost entirely fresh specimens. This plan I have followed because of the readiness with which post-mortem change sets in. Like other recent observers I have used uteri removed entire or specimens of the mucosa obtained by curettage. Specimens exhibiting a deviation from the well-established normal state of the glands, stroma, and vessels have been rejected. This has left, out of a much larger bulk of material, 3 complete uteri removed by operation, and 20 scrapings. In many cases the examination has been carried out with the aid of serial sections. In this section many references are made to the specimens of the premenstrual and menstrual phases of the mucosa. (Page 88).

In /

In the ordinary resting state the interglandular stroma is seen to consist of large numbers of cells. The nuclei are, for the most part, round or oval and are frequently so densely packed together that only a comparatively small amount of cell protoplasm is visible. Under higher magnification the nuclei are seen to possess, in most cases, a close chromatic network. With special methods of staining some of the nuclei stain with acid dye, others with the alkaline dye. The protoplasm of the cells is in some cases granular, in other cases sponge-like in nature. There is no evidence of a cell-membrane; in fact in many cases it looks almost as if the meshes of the protoplasmic sponge communicate with the surrounding intercellular spaces. In many cases the outline of the cells is very irregular and ragged. Intervening between the cells there are distinct intercellular spaces; across these, however, the cell-protoplasm is found to pass as strands, in this way establishing a direct protoplasmic communication between the contiguous cells. (Figures 1,2,4,8.) These strands vary in thickness; in some cases they are stout, in other cases they are represented by the very finest filaments. It is often possible to recognise that these fibrils are composed of granules /

granules similar to those in the cell body, which are set in a line, sometimes in single file. The intercellular spaces are usually clear; in other cases they are occupied by an amorphous material which takes on a faint eosin stain. These spaces, as suggested by Leopold, in all probability contain lymph, which in the latter case has become coagulated. In some cases portions of the stroma here and there may be seen to be represented by masses of protoplasm containing several nuclei - the differentiation into cellular units usually present becomes lost. This is an unusual condition and is probably not to be considered as anything but rare in the normal resting stroma.

The communication between adjacent cells is brought out more clearly in oedematous conditions, where the cells are spread apart; the protoplasmic filaments bridging across the enlarged intercellular spaces then become elongated, giving to the cells a distinctly stellate appearance.

(Plate I). In many cases this protoplasmic communication is represented by a fine network uniting the contiguous cell surfaces. In some conditions this protoplasmic mesh-work may be present over a comparatively large area from which the nuclei and cells proper seem to have disappeared. This appearance may partly explain why some writers have been /

been led to look on it as a tissue independent of, or at any rate, not in direct structural continuity with the cells. Leopold and others, as already mentioned, have considered the stroma as consisting of cell units entangled in its meshes. None of my specimens have suggested anything to lend favour to this conception; on the other hand it is nearly always possible with careful focussing to determine that the fine filaments in the proximity of a cell amalgamate with its protoplasm and that, in reality, the network consists merely of finely drawn out and branching portions of the cell substance. In support of this view, in addition to the above observation, may be mentioned the fact that it is often possible to determine that the amount of perinuclear protoplasm is inversely proportional to the number and length of the surrounding fibrils, suggesting that the body of the cell is drawn on to furnish the substance of the network. Further, in the course of this investigation, reasons will be adduced to indicate that if the communicating fibrils are torn across by any process leading to an enlargement of the intercellular spaces the drawn-out protoplasm may be retracted within the cell-body.

From these observations it will be obvious that the protoplasm of the stroma is a very variable /

variable structure. In some cases it is represented by a sort of multinucleated plasmodium, in other cases, and this is the normal state, the individual cells, though separated from one another by intercellular spaces, or found attached by bridging processes of a simple nature. In still other cases the protoplasm of the cells is drawn out to form branching processes united to produce a fine and intricate network.

The structural differences between the stroma cells are found to involve the protoplasm of the cell bodies chiefly. The nuclei, however, are found to exhibit many and diverging differences in staining character, size and shape. The alterations in the staining properties and size will be referred to more fully in the course of this investigation; suffice it for the present to state that any condition leading to an oedematous state of the stroma with an opening out and separation of the cellular elements is apt to be associated with an increase in the size and a diminution in the quantity of the nuclear stain absorbed. The variations in shape which the nuclei exhibit have led many observers to recognise and describe cells of different kinds. In some of the cells the /

the nuclei are round, in others, they are oval, in still others, they become drawn out into rods. It seems more rational to explain these structural differences as representing changes in cells of the same order, due in the main to mechanical influences. A striking and convincing proof of this statement is as follows:- In the ordinary resting state the interglandular connective tissue, say in the superficial part of the mucosa, is composed of cells densely packed together. The nuclei are round or oval and in the main the shape assumed by the surrounding protoplasm is determined by the shape of the nucleus. Where the cells are most densely packed together one finds that the oval or rod-like nuclei predominate, whilst where the tissue is more open the nuclei and cells approximate more to the round shape. Further, round the glands and round the vessels one not infrequently discovers the cells and nuclei drawn out tangentially and arranged round the lumen of the gland or vessel in concentric layers. Immediately bordering on the gland, the stroma cells are sometimes markedly flattened, the nuclei are represented by fine rods which nestle close up to the epithelial cells; they then constitute the so-called Basement Membrane of the gland (Figure 5). At first sight these well-marked /

well-marked differences in contour would justify the conclusion that we are dealing with cells of different orders, such as are described by many writers, (vide summary of literature.). This conclusion, however, is strongly negatived by the fact that in the presence of certain normal functional changes in the mucosa, these cell differences become obscured and often disappear entirely. If we still, for the sake of argument, limit our remarks to the more superficial portion of the mucosa (though, it should be noted, the same statements apply to the other regions,) we find that during the premenstrual stage in which the mucosa becomes greatly thickened due to an opening out of the stroma spaces by an oedematous escape from the blood-vessels which precedes the exodus of the more solid constituents of the blood, the cells assume for the most part a round or stellate character. (Plate I and Figures 1,4,11). The point of importance is that the previously existent discrepancies in form have become greatly diminished and in most parts completely lost. The only feasible and logical conclusion from this observation is that the cells of the stroma in reality consist of units identical in structure and, as far as our present knowledge can carry us, of units possessing a /

a similar function. A possible exception must be made to this general statement in view of the observation previously recorded, namely that the nuclei of some of the cells take on the acid stain, while others absorb the alkaline stain. Of the significance of this condition we are still unable to advance any conclusive statement; the attitude of pathologists would seem to be in the direction of considering it an indication, in other regions, not of the existence of cells of a different order and function, but of the presence of varying phases in the life history of the same class of cell.

The stroma is seen from the above observations to approximate closely in structure to the developing mesoderm of the embryo, which consists of imperfectly differentiated cell units united with one another by branching protoplasmic filaments. The microscopic appearances presented by the stroma, and especially the homogeneous character it exhibits on certain occasions, justifies the conclusions of many observers, namely that it consists merely of an undifferentiated embryonic connective tissue. Like the embryonic mesenchyme it is perhaps best considered as consisting of nucleated masses of protoplasm anastomosing with one another by means of finely /

finely drawn out parts of the perinuclear substance. Like the mesoderm of the embryo, also, the consistence of the protoplasm is probably more fluid than solid, in all likelihood, approximating to that of a soft jelly. This point will be again referred to later on. It seems likely that the many variations in shape of the cell bodies and nuclei are to be accounted for by their ready response to any mechanical influence, and that when these are removed, as in the premenstrual phase, the cells are able as it were to draw themselves together & assume the contour of the characteristic round or stellate condition.

The condition described in relation to the stroma cells in general applies with equal force to the, at first sight, differentiated cells surrounding the glands - the so-called Basement Membrane, and those arranged round the vessels in concentric layers. Where the stroma elements are separated by oedema or where the glands have shrunk away from the surrounding tissue, the elongated appearance of the nuclei and cell bodies is frequently completely dispelled and the cells are then seen to be identical with the neighbouring stroma cells. (Figures 5 & 6). This observation suggests that the apparently specialised cells of the Basement Membrane have been moulded /

moulded to their shape simply by being pressed up and flattened against the gland cells and that, when this mechanical influence is removed, they are permitted to draw themselves together. No other interpretation so far as I can see can satisfactorily account for the appearances. Precisely the same description applies to the stroma cells surrounding the blood-vessels. As already mentioned, the stroma round the vessels in all parts of the mucosa is represented by concentric layers of elongated cells with oval or rod-like nuclei, this appearance becoming gradually replaced by the irregular disposition of the cells as the vessel is left. (Figures 8, 9). Here again, where the stroma cells are separated by a watery exudate these appearances vanish completely, and the vessels are seen to be supported by cells differing in no respect from the ordinary stroma cell.

The following observations, whilst perhaps more appropriately studied in connection with the changes which the mucosa undergoes during menstruation, must be mentioned in this place in order to bring out one of the important characteristics of the stroma. That the consistence of the mucous membrane of the uterus is that of a soft, easily damaged structure is well-known. It can be scraped with ease from the underlying firmer coat of muscle. The /

The study of the microscopic character of the stroma furnishes us with important knowledge in this connection. Under ordinary circumstances, as already noted, the stroma consists of closely packed cells and the appearances then revealed by microscopic examination suggest at first sight that the stroma consists of a fairly compact and firm material. The study of the changes involved in the production of an oedematous or watery opening up of the tissue is found, on the other hand, to warrant the conclusion that the consistence of the stroma is, or at any rate, can easily become, more that of a soft, almost fluid medium. The nature of the displacement and spreading apart of the stroma elements in oedematous conditions, is, perhaps, best studied in the immediate vicinity of the vessels. In these regions we frequently find the stroma cells becoming detached, apparently with ease, in concentric layers. The less supported outermost cells away from the vessel lumen become loosened more readily than the densely packed cells which immediately abut on the vessel-walls. After the displacement of the outermost cells there can occur a similar loosening and teasing out of the inner cells. This condition would seem to correspond to a uniform and universal fluid escape round the vessel circumference. (Fig.

In still other cases the stroma cells appear to become ploughed up by the oedematous escape from one part of the vessel wall, and in this way a clear tract is created leading directly from the vessel-lumen into the surrounding tissue. (Figure 30)

In this process the stroma cells are apparently readily displaced to either side by the escaping fluid. In still other cases the cells of the stroma in the neighbourhood of the vessel concerned are seen to radiate from the vessel-wall, apparently wheeling into the line of the escaping fluid. It is often possible, in these cases, to recognise that the cells are, as it were, lifted off in a layer from the vessel wall. This condition, when present, is found to involve the cells immediately external to the intima, and can occur only after the more external stroma cells have become displaced. The cells thus lifted off like a flap from the vessel wall in reality correspond to a sheet of protoplasm. Exactly the same applies to the separation of the cells in concentric layers. These observations demonstrate in a convincing manner the soft displacable nature of the stroma protoplasm. The nuclei, which may be considered to correspond to more solid particles suspended in this semi-fluid medium afford a ready index to positional changes /

changes in it.

In addition to the stroma cell, easily recognised by its branching protoplasmic filaments, round cells, with comparatively large nuclei and a smooth regular surface, are usually visible. These lie free in the stroma spaces, singly or in numbers, and in all probability correspond to leucocytes of the lymphocyte type. A careful study of my specimens has convinced me that, under normal conditions, the presence of those masses of leucocytes or lymphoid nodules, described by other observers, is only rarely detected. On Figure 7 is shown such a nodule. In addition to leucocytes even in a normal resting mucosa, blood corpuscles are not infrequently encountered lying in the intercellular spaces of the stroma. These are of much more frequent occurrence towards the free surface of the mucosa and where present are usually in the proximity of a blood-vessel. It seems likely that the intercellular spaces are occupied, as suggested by Leopold, by lymph, which in some cases becomes coagulated to form the finely granular amorphous substance often detected. Under abnormal circumstances one not infrequently discovers the deposit of filaments of fibrin in the spaces.

STRUCTURE OF THE BLOOD-VESSELS OF THE
UTERINE MUCOUS MEMBRANE.

The uterine mucosa is provided with an exceptionally rich supply of blood vessels. The arterial twigs reach the mucosa as the continuations of the smaller arteries found at the surface of the muscular coat. They pursue a tortuous course through the stroma, giving off small branches en route. In many cases the tortuous nature of the arteries is so intricate that such a sinuous vessel when cut across in successive parts of its course in the same section may give the impression of a bunch of arteries closely set together. For the most part the arteries appear to traverse the entire thickness of the mucosa and do not break up into their capillary terminations till they reach the surface. Here these are not infrequently found to lie immediately subjacent to the surface epithelium. In many places, also, small branches are seen to lie in close proximity to, sometimes immediately in contact with, the epithelial cells of the glands. When the vessels are distended this appearance is often brought out more clearly and under these circumstances the vessels often seem to be more numerous /

numerous in the neighbourhood of the glands than in the surrounding stroma. The blood is carried back by venous channels to the muscular wall of the uterus. The veins, for the most part, are found in the proximity of the arteries, and like these, pursue a tortuous course.

In the resting state of the mucosa, as already mentioned, the vessels are convoluted, sometimes markedly so. It is interesting to note that in any condition which leads to an increase in the thickness of the mucosa, such as in the premenstrual stage, the vessels become drawn out, the flexuosities become opened out, and they are then seen to follow a course often perfectly straight for a considerable distance, a state which they never exhibit in the resting phase of the stroma. (Figures 11, 12). The rationale of this is readily understood by a reference to the diagrams appended. (Figure 22). In the first figure is represented schematically a tortuous vessel pursuing its way through the collapsed mucosa corresponding to the resting stage. In the other figure is shown how a swelling of the mucosa, such as occurs in the premenstrual phase will result in a drawing out and straightening of the vessel, which will again assume the /

the tortuous state with a sinking together of the mucosa.

STRUCTURE OF THE MEDIA OF THE VESSELS OF THE ENDOMETRIUM.

In the resting state of the mucous membrane the vessels are lined by a layer of flattened cells, which are drawn out in the long axis of the vessel, corresponding to the direction of the blood flow. This is the usual condition, but not infrequently the blood is contained in channels, whose immediate wall is formed by cells indistinguishable from the ordinary stroma cells; in these cases it looks as if the blood is contained in no proper blood-vessel, but is simply channelling the stroma. (Figures 22, 30 and Plate I.) The lining-cells are supported, on their outer aspect, by cells which, in most places, are identical with the typical stroma cell. In some places, however, they are drawn out to encircle the vessels as concentric layers of a varying number. In this way the mucosal vessels exhibit apparently specialised walls, of differing thicknesses, resembling those of arterioles in other parts. (Figures 2, 9). This concentric arrangement of supporting cells round the blood-vessels is often very strikingly brought out in /

in pathological conditions. (Figure 46).

When this appearance is present it is seen to become less and less marked as the region of the vessel wall is left; the concentric arrangement gradually fading away and becoming replaced by the more irregular disposition of the stroma cells. Whilst at first sight these cells look like cells more or less specialised for the performance of their supporting function, it seems probable that they consist, in reality, merely of stroma cells modified in no greater degree than can be easily explained by mechanical influences, in the same manner as the cells immediately bordering on the glands and surface epithelium are often flattened out by their being impressed on the flat surface of the bases of the epithelial cells. In structure and staining characters the cytoplasm and nuclei of these cells differ in no respect from the surrounding cells of the stroma. Like these, they are connected with one another and with the surrounding cells of the stroma by means of protoplasmic filaments, a condition brought out with especial clearness after an oedematous teasing out of the stroma, such as will be subsequently described in connection with the process of menstruation. (Plate I). A /

A fact which brings home in a convincing manner the identity of the cells forming the vessel wall (and at the present moment we are still discussing all the cells external to the endothelium,) and the ordinary stroma cells is that under these circumstances where there is an cedematous opening up of the stroma, all the differences previously existent, even those of shape and contour, become completely dispelled. During the premenstrual swelling of the mucosa it is interesting and convincing to note how the cellular distinctions become levelled, and this in every part of the stroma which exhibits the cedematous change. The ease with which this alteration in cell form is accomplished would appear to warrant one conclusion, and one conclusion only, namely that the apparent differentiation of the cell under discussion indicates a change merely due to environmental circumstances, and that with the removal of these the cell differentiation disappears. It seems not unlikely that the lateral pressure exercised by the blood in the vessels is sufficient to explain the appearances, this will act in such a way as continually to tend to open out the vessel walls. With the soft, pliable nature of the stroma substance this pressure is readily transmitted to the surrounding cells.

This /

This description of the vessel walls, with an occasional exception to be presently mentioned, applies to the vessels in every part of the mucosa, from the deepest incursions of the stroma into the superficial part of the muscularis to the free surface of the mucosa. It applies equally to the largest and best-supported vessels and to the smallest and most tender vessels at the surface. This investigation, then, into the appearances presented by the vascular walls during the changing states of the mucosa reveals the fact that the supporting cells, if we are to trust to the evidence acquired by the aid of the microscope, are identical with those forming the mass of the stroma. If possessed of a specialised wall at all, they must possess it only by virtue of the fine single-celled internal lining. Our research so far drives us to the conclusion that the vessel-walls are so constructed as to resemble those of capillaries in other regions of the body, or, at any rate, the fact that the support is formed only by the elements of the soft, mobile stroma which can easily become lifted off, proves that they differ widely in structure from vessels of a similar thickness in other parts of the body. The fact that structure elsewhere /

elsewhere is always adapted to function would indicate that the remarkable appearances just noted are, in all probability, intimately bound up with the functional changes which the uterine mucosa undergoes during menstruation and pregnancy.

On Plate I is represented an area of the uterine mucosa in the premenstrual stage. The stroma cells are separated by an cedematous exudate, which brings out clearly the structural appearances which I have described. Throughout the section figured there has been, except in the immediate proximity of the vessels, a complete disappearance of the many and varied differences in cell form which are found in the resting and condensed state of the stroma. Instead of this the cells are found to have approximated to one type, the stellate cell. The adjacent cells are seen to be intimately connected with their neighbours by means of branching protoplasmic processes, and the figure brings out in a very clear manner the constantly observed condition, that, except in the immediate proximity of the nucleus, the stroma protoplasm is broken up into a very intricate network. The meshes of this vary greatly in size; some are discernable only by the aid of a high-power lens, whilst others are so large as to be /

be seen easily with a low-power of the microscope. In fact, the appearances present would seem almost to justify the conclusion that the intercellular spaces are in reality of the same order as the meshes of the network and like them consist merely of fluid spaces in the undifferentiated protoplasmic mass, which forms the stroma.

On the plate are represented two vessels, or rather two different levels of the same vessel. Both parts are distended, the upper more than the lower. The point which I wish more especially to indicate in this place is the fact that the opening out of the stroma has involved the region in the immediate vicinity of the vessels, and here it is obvious that we are dealing with the same undifferentiated nucleated protoplasm. In the portions of the stroma in this specimen, as also in others exhibiting the premenstrual condition, where the teasing out of the cells by the oedema has occurred, there is invariably present the same change in the vessel walls. In no place can we detect the condensed arrangement of the stroma in concentric layers such as one sees in the resting mucosa.

As can readily be understood the position just taken with regard to the structure of the vessels /

vessels would be effectively weakened by the discovery of any muscular, fibrous, or elastic tissue as a structural component of their wall. With regard to muscular tissue there is a concensus of opinion in the literature that in no part of the mucosa, except occasionally in the vessel walls in the stroma immediately abutting on the muscularis, is there ever present muscular tissue. This my specimens fully confirm. It has been likewise clearly established by previous research that in the normal mucosa there is never found a formation of fibrous tissue. The nearest approximation to fibrous tissue is found in the spindle cells and their intercommunicating processes of soft protoplasm. The true nature of these elements I have fully discussed.

ELASTIC TISSUE IN THE ENDOMETRIUM.

So far as I can discover there has been no exhaustive study in the literature in the direction of determining the exact quantity of elastic tissue present in the mucosa of the uterus. In none of the papers to which I have referred in the summary of the literature of the subject is it even mentioned. This, in view of the otherwise exhaustive nature of some of the investigations, (Leopold, Möricke, etc.) is rather a remarkable omission. Most of /

of the research in this connection has been concerned with the location and quantity of the elastic tissue in the muscular wall of the uterus, to which a notable contribution has been added within the last few months by Pankow. This author in a short paragraph touches on the site and amount of the elastic tissue in the mucosa, and, as his research is especially important from the point of view of the present discussion, I shall refer to it somewhat in full. Pankow¹⁶ says, "Whilst in the mucosa, which has not yet begun to menstruate, of which, amongst numerous others, is one especially of a 17 year old girl, the elastic tissue in the vessels is either completely absent or is present in a few places as a very fine elastic interna visible only with the oil-emersion lens, in the virgin menstruating uterus of a like age, one finds quite a different condition. Instead of the rare presence of a very fine elastic interna one sees now a thicker elastic layer in almost all the vessels The elastic interna is not only thickened, but the elastic tissue is present also in the media as a more or less completely encircling elastic layer, which is connected with the internal elastic lamina by means of fine fibrils. When these changes have still further progressed we can see the whole /

whole wall surrounded with a dirty, greyish-blue elastoid mass, and it is then impossible to determine whether we are now dealing with an artery or a vein. In a 20 year old virgin I found these changes in a small vessel immediately under the surface of the mucosa, whilst it was completely absent in the deep layers." Weigert's stain was employed by Pankow to distinguish the elastic tissue.

For the purpose of testing the validity of these investigations I have examined all my specimens. To detect the presence of elastic tissue I have used Weigert's stain throughout. In all the sections of the normal mucosa, (including 23 in the resting stage, 3 in the premenstrual stage of swelling, 7 during menstruation, and 2 immediately after), there was a complete absence of elastic tissue in every part except, for the most part, in the deepest incursions of the stroma into the superficial portion of the muscularis. Here it was situated only here and there in the walls of the thicker vessels as a fine lamina just under the intima. It is completely absent in the surrounding stroma. Rarely the same appearances are detected in the deepest part of the stroma just external to the muscular coat. In no place were they encountered in the upper two thirds of the mucosa.

Whilst/

Whilst the number of the specimens just cited would seem to justify a conclusion in direct opposition to that of Pankow, I have reinforced these observations by the same investigation in 40 other specimens of the uterine mucosa which I have been able to obtain through the kindness of Dr.

James Ritchie, of the Royal College of Physicians Laboratory. These consist of scrapings obtained by the curette which were sent in for reporting and naturally comprise a large number of a pathological nature. Many of them, however, (10 in number) were, so far as microscopic characters go, perfectly normal; the rest exhibited such abnormal conditions as oedema, haemorrhage, and dilatation or hyperplasia of glands, none of which, I maintain, could have any influence in the direction of diminishing the elastic tissue present. In these specimens the examination was identical in every respect with that above-stated. The results in a tabular form work out thus:-

No Elastic Tissue found in the Upper Two-Thirds
of the Uterine Mucosa in.

33 specimens in the Normal Resting Condition.

3 " " " Premenstrual Stage.

9 " during Menstruation or immediately after.

11 " With oedema and haemorrhage.

19 " With glandular dilatation or hyperplasia

75. TOTAL.

On /

On the strength of these observations, I think we are justified in stating that the existence of elastic tissue either in the vessel walls or in the stroma of the upper regions of the Uterine Mucosa is, if ever present, of rare occurrence.

These investigations are in complete accord with the vascular changes which I have previously noted. In the beginning it seemed to me unlikely that vessel walls, which can open up in the remarkable manner described, could possibly be equipped with the support which an elastic tissue layer would imply.

So far, then, we have seen that for some reason or other the uterine vessels almost immediately after reaching the mucosa throw off their specialised supporting coats. Here their walls external to the intima are formed entirely by the elements of the soft, mobile stroma, which in the thicker vessels is somewhat condensed to form a pseudo-media of varying thickness. Under certain circumstances, which have been indicated and the importance of which will be studied more in detail subsequently, the cells of this pseudo-media can become easily detached.

STRUCTURE OF THE INTIMA.

The/

STRUCTURE OF THE INTIMA.

The flattened cells which form the immediate lining of the walls of the mucosa vessels appear at first sight to be of the nature of a true endothelium, such as is found in other regions. That a specialised endothelial layer, however, is not an essential structural component of the stroma vessels is suggested by the fact which I have previously mentioned, namely that in many regions the lining of the vessels would seem to be formed simply by unaltered stroma cells. In these cases the vessel-wall often seems on examination to be constituted throughout its entire thickness of cells resembling in all respects the ordinary stroma cells. (Figure 28).

This observation, which one sees occasionally noted in the literature of the subject, suggested to me a line of enquiry in the direction of determining if possible whether the flattened cells found in most places forming the internal vessel lining are, in reality, to be considered as a specialised endothelium, which histological text-books indicate is an invariable component of vessels in other regions. These investigations, which have been carried out in a considerable number of uteri exhibiting all the phases in the functional variations to which the mucosa is subject, have convinced me that here again we are dealing, not with cells, which /

which were in the course of their development bound to become specialised as an endothelial lining, but with cells which, in every respect except, perhaps, in a way which is easily explained by the mechanical influence of the blood stream, correspond to the stroma cells. As already mentioned the protoplasm of the mucosa cells has retained its soft and pliable embryonic consistence. It is drawn out with ease into long tender filaments and it adopts with facility any shape impressed on it by any extracellular pressure. If packed together the stroma cells and nuclei are apt to assume an oval or rod-like contour; when, on the other hand, the tissues become opened out the cells and nuclei tend to assume a more spherical shape, that namely, characteristically chosen by cells free from unequal extraneous pressure, e.g. leucocytes.

The lining cells are seen, under the microscope, to be connected with the immediately adjacent cells by means of protoplasmic filaments, in this way, establishing a resemblance to the typical stroma cell. (Plate I and Figure 11). The nuclei of these cells are found, in sections which cut the vessel longitudinally, to be drawn out in the long axis of the blood-vessel. In staining character and in structural appearances the resemblance /

resemblance between the lining cells and the surrounding stroma cells is perfect. In some cases, as already mentioned, the intimal cells are not even flattened out like an endothelial lining and correspond in every respect, even as regards shape, to the stroma elements. (Figure 28). The protoplasm of the lining cells is granular in appearance; in some cases, like the stroma cells, it may exhibit a sponge-like character, and here again the meshes of the sponge often seem under the oil-emersion lens to open out into the vessel lumen.

When the stroma cells become loosened and separated from the vessel wall by means of an oedematous exudate, the resemblance between the so-called endothelium and the adjacent cells becomes even more manifest. With these they are seen to communicate by means of long protoplasmic strands or by means of a fine network. When the endothelial layer of the vessel is cut across tangentially it is often impossible to distinguish in any way its component cells from those of the adjacent stroma. Under such circumstances, in conditions where the intercellular spaces of the stroma are increased in size, (e.g. during menstruation) it is often easy to discover the presence of similar spaces between the endothelial cells.

These /

These appearances are well brought out in Plate I. At the regions in the vessels corresponding to the levels a, f, and g, the endothelial layer is cut tangentially. The structural similarity of the cells to the adjacent stroma elements is convincingly demonstrated. At these regions the lining cells are often seen to be separated by spaces similar to the intercellular spaces of the stroma. In these red blood corpuscles are often seen to be situated. Appearances similar to those are shown in Figures 3 and 4. These observations at first sight strongly suggest that, in the opened-up stroma, the cells forming the vessel lining are separated by distinct intercellular spaces, and that, in this way, the vessel lumen communicates directly with the adjacent meshes of the stroma. As will be subsequently described it would seem to be through these spaces, which have become enlarged, that the blood corpuscles make their first escape into the surrounding stroma during menstruation. Through these interstices between the cells individual blood corpuscles are often seen escaping and on tracing a blood track back to the vessel the red cells are often seen streaming in quantity into the adjacent stroma.

As is well-known the uterine stroma is peculiarly liable to an oedematous or watery loosening/

loosening and separation of its constituent cells. This condition is frequently detected in places in a mucosa in the resting stage which is perfectly normal in structure; as will be described in a subsequent section of this investigation it occurs, also, as a normal process in the premenstrual and menstrual mucosa and it would, in addition, seem to be a precursor of the decidual enlargement of the stroma cells in pregnancy. Its occurrence, also, is frequently noted in some pathological conditions. Whilst these facts will be studied in greater detail in a later part of this investigation, they must be noted here in reference to their bearing on the question of the real structure of the lining cells of the vessel. During the premenstrual and menstrual alterations in the mucosa, the vessels, especially those towards the surface, are found to dilate, sometimes to a considerable extent. In addition to this, however, they are often seen to open out by an entirely different process; the adjacent stroma cells become teased apart, the lining cells part company with one another and, as it were, step back to range themselves alongside the displaced stroma cells. (Figures 29, 30). Under these circumstances it is impossible to tell which are the original intimal cells and which the stroma cells/

cells. The displacement of the cells in this process entails the severance of the intercommunicating protoplasmic fibrils binding them together. When this occurs, it seems that the protoplasm is withdrawn within the cells, which then assume a more rounded contour. They lose completely their original flattened appearance and identify themselves in every respect with the surrounding cells of the stroma. These facts suggest strongly that the flattened, endothelium-like shape which they present is one not only impressed on the cells by mechanical influences, but is one from which they recover quickly when this influence is removed. They thus correspond closely with the so-called basement membrane of the glands. This is often constituted by a row of markedly flattened cells which abut on the gland cells. These are, as already demonstrated, in all likelihood, not specially differentiated cells but merely cells of the stroma flattened against the gland - they lose their flattened appearance when released from the pressure. It is likely that the same considerations apply to the so-called endothelial cells of the stroma. These appearances are all shown on Plate I, which represents a condition of common note in the normal premenstrual mucosa. At the /

the levels marked d and g . the vessel walls are seen to be opening out. The flattened endothelial layer, possessing its ordinary characters at c, is seen at d. to have opened out and to have been carried alongside the stroma cells to aid in the formation of the confines of the newly created blood space. Here it is impossible to tell which is original endothelium and which is stroma cell. The same appearances are detected at other parts of the vessel walls. In figure 24, also, are shown the changes associated with an opening out of the vessel walls. On one wall of the vessel, which has not shared in the process, the drawn-out flattened cells of the intima are visible; on the other wall, in which the process is well-marked, it is impossible to distinguish between the inner cells and the cells of the surrounding stroma.

I have previously demonstrated the fact that the walls of the vessel external to the endothelial layer are formed exclusively of stroma cells sometimes compressed together to lend greater support to the wall, but otherwise identical with the stroma cells. In this way we were led to the conclusion that the vessels of the stroma of the uterine mucosa must be considered to correspond in structure./

structure to capillary vessels in other regions. I have now advanced facts to prove that the so-called endothelial layer is, in reality, not composed of specialised cells but merely of stroma cells, in some cases flattened like a true endothelial lining, whilst in other cases it consists of stroma cells unaltered even in form. In the subsequent sections of this investigation still further evidence will be adduced in support of the contention that the intimal and the stroma cell are structurally and functionally identical. From the foregoing observations, it would thus seem likely that the blood flows through the stroma, not in properly formed blood-vessels, but simply in channels which it has formed for itself in the soft, mobile protoplasm of which the stroma is constituted. This has become displaced, probably with ease, in the formation of the blood track.

If, as these observations indicate, the so-called blood-vessels of the endometrium are, in reality simply undifferentiated tracks through the stroma, we would expect to find that the larger vessels in the deeper part of the mucosa would conform in structure with the fine capillary twigs towards the surface. That this is the case is a fact of easy demonstration and as I have pointed out /

out, it is interesting and instructive to note that the comparatively thick-walled arterioles in the muscle wall with a distinct endothelial lining and a wall formed by muscle cells and elastic fibres apparently throw off their supporting coats almost immediately the stroma is reached. In none of the specimens is there any evidence of muscle, fibrous or elastic tissue in any part of the uterine stroma, except that adjacent to the muscular coat. Where the vessels require an extra support they derive it through a condensation of the neighbouring tissue cells.

In this place attention must be called to observations made by Leopold in connection with the structure of the stroma of the uterine mucosa. In his work he has clearly demonstrated in the human subject and in some of the lower animals the structural resemblances between the intima and supporting cells of the vessel wall and the cells of the stroma. The great importance of this observation would seem to have been somewhat obscured by the fact that more recent workers on the subject have demonstrated the fallacy of Leopold's statement that the cells of the stroma consist of round or oval plates, for the most part, independent of one another. The connective tissue fibrils which often form a complicated/

complicated network we now know do not, as Leopold maintained, constitute a completely independent structural entity but are in reality merely drawn out processes of cell protoplasm.

These erroneous observations led Leopold to the belief that the cells are in reality endothelial plates, which, set side by side, form a continuous endothelial lining for the lymphatic sponge of which the stroma consists. The cells forming the walls of the blood-vessels are, also, according to Leopold, endothelial in nature; the thicker-walled vessels, as well as the finer, consisted throughout of these endothelial plates. I mention these observations of Leopold as they, to a certain extent, confirm my own investigations, although my research has led me to adopt an entirely different interpretation of the appearances presented.

Throughout this record it has been mentioned that the appearances presented by the mucosa at first sight suggest that the intercellular spaces form an intricate network of fine tracks freely communicating with one another, and that, in this way, the mucosa as Leopold first suggested constitutes
a /

a sort of lymph sponge. This interpretation of the structure is derived from two separate observations. (1). The protoplasmic connections between the cells are usually represented in section as fine filaments, and these certainly appear under the microscope like threads stretching across the spaces, and the conditions suggest that, whilst just sufficient to connect the adjacent cells, they do not interrupt the communication between two neighbouring spaces. (2). In the second place Leopold was able to inject this intricate system of spaces from the lymphatic trunks in the muscular wall of the uterus and under the peritoneum. Are these two observations necessarily to be taken as proof positive of the usually accepted interpretation of the structure of the protoplasmic network of the stroma? My investigations have more and more convinced me that on this subject we may have been rather hasty in acceding to the teaching of Leopold and subsequent observers in view of the somewhat flimsy nature of the evidence advanced. It is obvious that an apparently thread-like connection between two adjacent cells would be the appearance revealed in section if this protoplasmic communication were of the nature of a complete film. In this respect, therefore, the /

the evidence is not convincing. In the second place all that Leopold's experiments demonstrate with certainty is that between the uterine mucosa and the muscular lymph-vessels there is a tissue connection. The fact that colouring matter injected under pressure disseminated itself throughout the stroma does not necessarily prove the fact that the tissue spaces are in complete continuity. It is clear that a minimum pressure would suffice to rupture the fine protoplasmic films if such existed. Whilst the experiments prove all that Leopold desired to show, they no more convincingly and indisputably substantiate the orthodox conception than would the rupture of a soap bubble with a pin prick prove that the interior of the bubble was previously in direct communication with the outer air.

Whilst on such fine histological details it is impossible to dogmatise, I would submit the following observations in favour of the idea that the communications between the stroma cells are not of the nature usually supposed, i.e. threads of cell-substance, but may in reality consist of protoplasmic films and that each of the intercellular spaces, in the resting state of the corresponding portion of the mucosa, is in this way completely shut in on every side.

(1) I have shown how in the opening out of the vessel walls, the endothelial cells are able to step back and range themselves alongside those of the stroma. (This I shall refer to in greater detail in the section on the Menstrual Changes). Under these circumstances, there is often an associated teasing apart of the stroma elements, with a marked widening of the intercellular spaces. According to the usually accepted idea, this opening up of the stroma should result in a freer communication than ever between the fluid tracks. The teasing out of the intimal cells is necessarily associated with a separation of the intervening connections. The result of these changes is that in the end the vessel wall is formed almost entirely of the stroma elements separated by the intercellular spaces, which, if the ordinary conception be correct, open directly into the vessel-lumen, and by apertures much larger than the intercellular spaces of the resting stroma. Is this so? As we have shown these changes result in a marked expansion of the vessel lumen and this, in its turn, must be associated with a distinct increase in the lateral pressure of the blood fluid. This we would expect to determine at once a liberal and universal escape of the red cells into the adjoining tissue through the perforations in /

in the wall, many of which are large enough to accommodate several red cells. The fact that this is not so, and that instead, whilst there has been a copious fluid escape, the red cells are for the most part retained in the lumen and can often be seen to lie up against the vessel wall, strongly suggests, I submit, that this is not perforated but complete. In several places, undoubtedly, the red corpuscles can be seen leaking through the wall, but this is only comparatively seldom, and only where a giving way of the tissue bridge between the lining cells can be seen to have given way (Plate I.) If my interpretation, then, of the mode in which these blood spaces are formed be correct, (and I shall substantiate it in the next section,) we have strong evidence in favour of the fact that the protoplasmic connections passing between the cells are complete films and not mere threads.

(2.) Another observation of weight with regard to this question is to be found in the fact that the protoplasmic bridges between adjacent cells are almost invariably seen to be complete in the sections i.e., one can almost always follow the wall of protoplasm completely round the intercellular space. This we can do both in the case of the small /



the smaller spaces and in the largest spaces. If these tissue bridges corresponded to filamentous processes we would almost certainly find that in sections they would be in places, and probably in many places, completely severed as the section cut them across. On the other hand, if they correspond to complete spherical films at various parts of whose surface the cells are situated, it is clear that no matter the plane in which the section is made, the intercommunicating bridges will be invariably complete. It seems to me that this observation of itself is confirmatory evidence of the strongest type in favour of the conception of the nature of these spaces which I have advanced.

From these observations, then, it seems likely that the intercellular spaces, which form one of the chief structural characteristics of the mucosa, do not freely intercommunicate to form an intricate and complete network for a fluid circulation, but are, in reality, each a separate and distinct fluid space or "vacuole" separated from its neighbours by a protoplasmic film. As the existence and nature of these spaces seems to me to be of the greatest importance from the point of view of the structure of the stroma and the functions which this subserves, it will be necessary to study them in greater detail.

STRUCTURE OF THE TISSUE NETWORK OF
THE STROMA.

As has been shown by a study of the literature, the existence of this fine network in the uterine mucosa early attracted attention. By many observers it is looked upon as a structural entity completely independent of the stroma, whilst by others, and these the most recent workers on the subject, it is recognised as consisting of drawn-out portions of the protoplasm of which the stroma is formed.

One of the most remarkable features of the stroma which my investigations have revealed, is the striking variability in appearance which this structure exhibits. In the resting state of the stroma, when the cells are usually closely packed together, the protoplasmic bridges are, for the most part, simple and unbranched. In conditions associated with a teasing out of the stroma, on the other hand, it is usually found that this structure assumes an appearance of the greatest complexity. Instead of the straight bridge-like process there is found between the adjacent cells an excessively intricate structure, on section /

section looking like a finely-spun network. Instead of the simple intercellular space there are found a large number of spaces varying greatly in size, the smallest only recognisable with the oil-emersion lens, whilst others are visible with the low power of the microscope. (Plate III & IV). These appearances will be discussed more fully in connection with the stroma changes in menstruation. In this place, however, an observation must be noted because of its importance in connection with the probable nature of the intercellular space. With the appearance of this intricate protoplasmic structure it is often seen that there is a diminution in the amount and even a disappearance of the denser cell-substance round the nuclei. In other words it is clear that the cell cytoplasm has been drawn on to furnish the material of which the network is formed. The spaces are filled with a clear fluid and, as I shall subsequently point out, it is likely that in this change we see the result of an active fluid imbibition by and displacement of the protoplasm of the stroma cells. The process in all likelihood is determined by an osmotic diffusion into the cell protoplasm, the soft embryonic nature of which is eminently adapted to allow of this occurring with ease. If such be the case the newly-created spaces /

spaces will correspond to those which are well-known to occur in hydropic distension of cells in other tissues, and which I shall subsequently illustrate with greater precision in the stroma cells. I mention these facts somewhat in anticipation for the purpose of indicating that in the intercellular spaces of the ordinary resting state and the intricate arrangement of fluid spaces which appears in an edematous stroma we are probably dealing with exactly the same structural conditions, i.e., fluid cavities for the most part completely closed in.

The structure of the stroma coincides closely in appearance with that of the mesodermic tissue of the developing embryo, and it has for this reason been considered by many observers as being nothing more than a primitive or embryonic connective tissue. This conception of the stroma my investigations amply confirm, but they have carried us still further in indicating that the lack of differentiation applies with equal force to the blood-vessels as to the surrounding stroma, and that, in fact, the vessels consist in their entirety of ordinary stroma cells, which, if altered at all, are simply altered in a way easily explained by the influence of the blood stream. The blood-vessels, in other words, have no specialised wall but consist merely of tracks /

tracks or channels through the soft stroma protoplasm, by means of which a rich supply of blood is carried to every part of the mucous membrane.

Stage by stage the researches here recorded have led to a conclusion in direct conflict with the orthodox conception of the capillary system in other regions of the body. (It has been shown that the blood vessels of the mucosa correspond closely in structure to capillaries in other parts.) This of itself did not deter me in my belief, especially in view of the fact that in other respects the structure of the stroma of the uterine mucosa must be considered to conform with, and correspond to, no other tissue in the adult human body. Enough I think has been shown in this investigation to confirm this belief. It seems not unlikely, also, that the usual description of vessels in other organs of the body may not necessarily apply to those of the uterine mucosa, especially when we recall to mind the functional changes which this structure presents. During menstruation there is a liberal opening-up of some of the vessels toward the surface; reasons will be adduced in a subsequent section of this record to indicate that the structural peculiarities of the vessels of the stroma and of the stroma itself are such /

such as to permit this to occur with the greatest possible efficiency. During pregnancy, also, there is an immediate and easy gaping of the vessels in the proximity of the embryo - the great perfection of this mechanism, also, would seem to be attributable in a large measure to the conformation of the vessel walls.

These two questions, namely the opening-up of the vessels during menstruation and the mode by which the developing ovum is furnished with its blood supply, will be discussed in subsequent portions of this investigation.

It would seem, then, not unlikely that unusual function may demand unusual structure. The fact that the construction of the vessels of the uterine mucosa follows a different order from that of vessels elsewhere in the body would seem to be amply accounted for by the remarkable functions which they have to subserve. It has, I think, been clearly shown in the preceding pages, a fact which, moreover, Leopold had convincingly demonstrated many years ago, that the portions of the vessel walls corresponding to the media and externa in other regions of the body are formed, not by muscle or connective tissue, but merely by stroma which is condensed in a measure proportional to the needs of the vessel, but in such /

such a way as to offer no obstacle to a ready gaping of the vessel when occasion demands. This structural peculiarity at once places the uterine vessels in a class by themselves, and, this proved, the structure claimed for the intima is rendered not so unlikely as it otherwise might be.

Some recent work on the comparative histology of the blood vessel system is of importance in this connection, and is suggestive in indicating that the cells entering into the construction of the vessel walls are not necessarily such as were bound to subserve this function in the course of their development, and that the so-called endothelium may, at least under certain circumstances, be derived directly from the connective tissue cells in the proximity of the vessel. It would tend, in other words, to indicate that the stroma of the uterine mucosa, which, after all, has for long been classified as a rudimentary tissue retaining its embryonic character, has its prototypes in the animal kingdom. From Dahlgren and Kepner¹⁷ in their "Principles of Animal Histology" I would quote the following suggestive paragraph.

"The main blood channel system itself has many differentiated regions. The region of thin-walled capillaries and lacunae, the strong-walled conducting /

conducting vessels, and the blood-forming organs and the muscular pumping stations or hearts ...
 Most specific of these portions are the capillaries and lacunae, for it is here that the region work of the blood is accomplished, the exchange of material with the tissues. Here the walls of the vessels are thinnest or even apparently wanting. In this case the connective tissue cells that surround the channel, while not differentiated into definite channel walls, act in that capacity, so that we cannot say that retaining walls are altogether absent.....

The internal tissue of a Turbellarian worm is a loose aggregate of several kinds of weakly differentiated cells, known as parenchyme. These cells do not touch each other at all points, but are connected by strands, and in consequence, there may be easily seen between them a great many spaces, known as the intercellular spaces, which are united into a large connecting system that extends throughout the body. This system of spaces is filled with a fluid, and this fluid carries the digested food materials, the oxygen supply for internal cells, the combustion products, and in every other way acts as a /

a simple blood-vessel. This is the undifferentiated, unorganised form of blood-vessel system and a sort of circulation must inevitably take place as a result of the ordinary movements of the animals's body. This grade of structure is to be seen in a number of the lower and simple animal forms, and sometimes as an accessory apparatus to several grades of complete blood-channel system"

In this description of a simple blood system we cannot fail to see a strong analogy to the structure of the uterine mucosa as figured in the previous pages. The comparative researches of these authors reveal so much evidence of value with regard to the investigations here recorded, that I cannot refrain from quoting still further from their interesting work. Their researches prove that,

"The intima may alone confine the blood stream, or, if the pressure is too great, it may be reinforced by the connective tissue cells that immediately surround it. These cells develop their connective tissue as fibrils or plates or webs with which they bind and hold the vessel intact when the blood presses on its walls."

This description corresponds accurately
to /

to the condition which we noted in the vessels of the uterine mucosa, with the exception that the development of a more specialised connective tissue in the walls occurs to a much less degree than is usually found. Again they say "all the cells and the tissues that they form were probably not cells that were bound in the course of their development to become so specialised, but as far as can be told, they were such of the connective tissue cells as happened to be in the course of the developing blood channel as it pushed its way among them, and were developed in response to the needs of the vessel."

The results obtained by Dahlgren and Kepner from a comparative study of the developing blood systems in various animal classes is of the greatest importance in relation to the origin of the different coats of the vessels in man, and they would tend to indicate that the hitherto widely accepted opinion that endothelium must develop from endothelium, muscle from muscle, etc, may require some revision in the immediate future. In any case their work seems to me to lend added feasibility to the conception of the vascular system of the uterine mucosa to which my researches have pointed. I may state that my conclusions had been definitely arrived at /

at and were distinctly formulated in my own mind before I had the opportunity of seeing the results of the work of these two investigators..

S U M M A R Y.

- (1) The stroma of the uterine mucosa consists of a soft semi-fluid protoplasmic mass imperfectly differentiated into cellular elements.
 - (2) The cells are separated by intercellular spaces, which together form a complicated system occupied with clear fluid (ordinary lymph according to Leopold).
 - (3) The cells anastomose freely with one another by means of protoplasmic processes. They present many and varying alterations in shape, but these are easily dispelled and the cells then approximate to the typical round or stellate shape. The differentiation of the stroma cells is, thus, probably more apparent than real.
 - (4) The intercellular spaces, in all probability, do not communicate directly with one another.
- The/

The anastomosing processes of the cells are probably not filaments but films of protoplasm, which under ordinary circumstances close in the fluid cavities.

- (5) The intima and media of the vessels, and the basement membrane of the glands are nothing more than ordinary flattened stroma cells. This shape they easily lose.
- (6) Except in the deepest layers of the mucosa the vessels have no specialised supporting coats (muscle, elastic tissue).
- (7) The vessels are obviously so constructed as to allow a ready and universal opening up of their walls, and the structure and consistence of the stroma such as to permit its ready displacement by fluid or blood. It would seem that these structural peculiarities must have some intimate bearing on the functional changes of menstruation and pregnancy.

SECTION I.

SECTION II.

MENSTRUATION.

CHANGES IN THE UTERINE MUCOUS MEMBRANE DURING MENSTRUATION.

LITERATURE. As was true in regard to the normal histology of the uterine mucous membrane, the microscopic changes present during the process of menstruation have been studied by many observers with numerous and conflicting results. Before proceeding to the results of my investigations it will be necessary to refer to some of the most important papers written by previous writers. As there is, so far as I could discover, in the English language, nothing more than short abstracts of the literature on menstruation, my study has necessitated a rather lengthy investigation, in many cases, of the original papers. As most of these are in German or French, I have thought it wise as far as possible, to include them in this compendium of the history of the subject. The order followed in the resume will be as far as possible of a chronological nature.

By the ancients many and grotesque ideas were entertained with regard to the monthly loss of blood. These do not at present concern us.

The first truly scientific treatise of the subject/

subject appeared in the middle of last century in the work of Bischoff¹⁸, Pflüger¹⁹ and others. By these authors the relationship existing between the rupture of the Graafian Follicle with the escape of the ovum and the changes in the uterine mucosa was first definitely formulated. As we shall have to refer subsequently to Pflüger's interpretation of the interdependence of the two processes it is necessary to summarise it here. According to him the growth of the cells in the ovary previous to ovulation leads to an increasing irritation of the nerve fibrils imbedded in the parenchyma. When the sum of the stimuli reaches a certain degree of strength a powerful reflex congestion of the genitalia is induced with the consequent blood escape from the uterine surface.

As regards the anatomical changes in the mucosa during menstruation, Pouchet²⁰ it would seem is the first author responsible for the assertion, that at each period a plastic exudate is formed on the inner surface of the uterus (decidua) which is thrown off if pregnancy does not occur. Bischoff's researches on the other hand demonstrated that the decidua is not entirely a new formation but is produced by changes in the mucosa of the uterus. ²¹Janzer in the case of a young woman who died shortly after menstruation noted a thickening of the mucosa and a lengthening/

lengthening and widening of the glands. The epithelial cells of the surface and of the glands had lost their ciliated margin. ²² Meckel noted a thickening and growth of the mucosa during menstruation, especially affecting the glands. ²³ Hennig described a softening of the mucous membrane which assumes a spongy structure; the glands are lengthened and become tortuous and the vessels are distended with blood. Frei² arrived at somewhat similar results. He saw in addition detached epithelial cells in the escaping blood. Hyrtil²⁴ declared that the epithelium of the surface is thrown off during the process, but it soon becomes replaced. Kölliker²⁵ described a softening and thickening of the mucosa, with the escape of blood from the ruptured superficial capillaries. There is present a detachment of the great part of the superficial epithelium with the exception of that of the cervix. This is found in the escaping blood.

The observations above recorded comprise the chief work done by the older writers. ²⁶ Sigismund in 1871 advanced the theory, which is still held, or has been held till recently, by many writers that "die menstruation ist ein abortus". He based his/

his theory on the supposition that the mucous membrane is thrown off at each menstruation period. The bleeding corresponds to that found in an ordinary abortion, and is associated with a discharge of the mucosa with the ovum. According to him the fertilised ovum corresponds to the ovulation period associated with the first monthly period missed. With the appearance of the work of Kundrat and Engelmann⁵ in 1873 a new era in the scientific study of the subject is opened and from that time onwards treatises on the changes in the uterine mucosa during menstruation follow one another in rapid succession. According to Kundrat and Englemann the process is associated with a swelling and softening of the mucosa. The softening occurs to such a degree as to make the mucosa almost fluid in consistence. There is injection in some places. The interglandular tissue in the upper part is richer in cells, due to an increase mainly of the round cells. Both kinds of stroma cells and those of the glands are multiplied. At the time and for some time afterwards the cells become turbid and are filled with fat-drops. This is present not only in the superficial cells of the stroma but also in those of the blood vessels and epithelium of the surface and the glands. They think/

think that the fatty degeneration is in all probability the cause of the bleeding. A large part of the surface and gland epithelium becomes detached.

The next important contribution to the subject is that of Williams²⁷ (Sir John). His material was obtained for the most part from patients who had died of acute infectious fevers, in all nineteen. There was fatty degeneration of the whole mucosa during menstruation: it begun at the os internum and spread to the fundus. The contractions of the uterus force the blood into the mucosa and as a result of the fatty change the vessels give way with a consequent extensive haemorrhage which results in a complete detachment of the mucosa. This is regenerated from the muscular coat. The process begins here again at the os internum and by the end of three days two thirds of the mucosa is restored; after a week the surface is completely covered by mucosa with an epithelial lining. The plain muscle fibres produce the spindle-cells, the connective tissue the round-cells, the round-cells the epithelium. Menstruation is not to be considered as a mere congestion but is rather a degeneration followed by bleeding./

bleeding. Underhill²⁸ in the uterus of a woman who died from apoplexy immediately after menstruation noted that only the superficial layer of the mucosa was absent. The glands were running obliquely or parallel to the surface and were present deep into the muscular coat. Leopold⁷, to obviate the risk of confusing changes induced by illness with those due to the menstrual process, used material only from patients who had died from sudden illness and accidents and who had had normal menstruation. He described the changes in the mucosa not only during, but before and after, menstruation. His work constitutes an important addition to the literature of the subject. According to him the mucosa undergoes a considerable swelling several days before menstruation - even to a thickness of 6-7 mm. With the onset of menstruation this swelling disappears and the mucosa returns to its usual thickness of about 2-3 mm. With the increase in thickness a marked folding of the surface occurs. Because of the falling together of the mucosa after the onset of the bleeding the uterine cavity is less encroached on during than just before the process. The swelling is due to (1) a multiplication of the endothelial plates -/

plates - the Zellplatten, which, as we have seen, are supposed by Leopold to constitute the main substance of the stroma: (2) oedema. By this the mucosa is opened out, and becomes softer. The glands increase in length and width, whilst the blood-vessels, until shortly before the onset of menstruation are not yet notably distended. In discussing the probable cause of the bleeding he disapproves of the idea of Kundrat and Engelmann that it is due to a fatty degeneration of the stroma, the vessel-wall, and the epithelial cells of the glands and surface. In support of this contention he declares that so long as the occurrence of a fatty change before the onset of the bleeding is not constant, it cannot be considered as the cause of the menstrual phenomena. In describing a specimen obtained a few days before menstruation he notes that the mucosa is swollen, it is quite intact and shows no fatty degeneration, nor distension of the blood-vessels. His explanation of the factors at work in the production of the bleeding is as follows:- As the result of the ovarian influence an acute hyperaemia of the uterus is induced. The blood-vessels become markedly swollen and this is facilitated by the softening and loosening of the superficial tissues, which occur during the/

the premenstrual phase. From the widened capillaries there is an escape of red and white blood corpuscles for several days into the immediately surrounding tissues and by this means the superficial epithelium and the epithelium of the gland-mouths are lifted off. The actual onset of the bleeding is determined, not as Williams declares by a degeneration and separation of the mucosa, but by the arrangement of the blood-vessels. Though the spiral nature of the arteries tends to slow the blood flow the vessels are markedly flushed and an increased quantity of blood is thereby carried to the superficial capillaries. Here again the blood stream is arrested, firstly through the enormous widening of the capillaries, and secondly through the sparse supply of venous channels in the mucosa. These two factors determine the free escape of the blood from the vessels on to the surface of the mucosa from which the superficial epithelium has been detached. Leopold maintains that, though the existence of a relatively poor supply of efferent blood channels in the mucosa has never been absolutely proved, certain conditions, which he cites, make it extremely probable. Further, with the escape of the blood and the oedematous fluid the mucosa collapses, the previously opened-out tissue becomes dense, /

dense, and the elongated gland tubules must double up and assume a spiral or corkscrew course. With the cessation of the bleeding at the fifth or sixth day, regeneration sets in, the superficial breaches of surface become filled in by an increase in the Zellplättchen, and the denuded epithelium is replaced by that lining the glands. "The mucosa undergoes changes to be likened to an ebb and flow and not a progressive and a retrogressive metamorphosis".

Möricke⁹, in 1882 published a treatise on the structure of the mucosa of the uterus, with which he incorporates a careful and elaborate investigation into the changes which occur during menstruation. This work marks a still further and important advance in our knowledge of the subject. The material on which the researches were based, was obtained from 45 women and includes every stage in the menstrual process. Many of the specimens were useless for the purpose because of the soft and pulp-like nature of the mucosa which renders it easily damaged by the curette. Under these circumstances the microscope reveals only the presence of masses of cells and free nuclei. He examined his specimens both in the fresh state and after hardening. In the fresh the epithelial cells have always retained their cilia, and/

and often deep into the glands. There is no trace of fatty degeneration either in the cells of the stroma or the epithelium. The body of the epithelial cells consists of the characteristic granular protoplasm with a round nucleus. There may be small fat drops present. The nuclei of the stroma cells are large and almost fill the cell body. There is little evidence of cell growth or cell division. In the hardened specimens the surface is seen to be wavy, the epithelium is intact, and that of the surface and of the glands is covered with a finely granular material. There are present blood extravasations at the surface, especially round the glands. A fact which Möricke lays especial stress on is the absence or only seldom occurrence of extravasated blood in the middle and deeper portions of the stroma- it is almost entirely found at the surface. The glands are very numerous, they are distinctly widened and run obliquely to the surface, often markedly twisted. There is no evident increase in the interglandular cells. They are often closely packed together, whilst the ground substance is markedly increased in amount. The vessels are greatly distended especially towards the surface. After recording the observations/

observations on his material he says that "by these researches the opinion advanced previously by C. Ruge that there is the occurrence of even only a partial shedding of the mucosa during menstruation has not been indisputably proved. The changes, which the mucosa exhibits, belong not to the class of the retrogressive metamorphosis but to a true congestion. The vessels expand, become filled with blood, and small extravasations are produced. The stroma become softer and sponge-like and assumes the condition which alone will prepare it for the reception of the fertilised ovum". For the explanation of the bleeding Pflüger's congestion theory is probably sufficient. The peculiar arrangement of the blood-vessels leads, as Leopold has shown, in the presence of the reflex arterial hyperaemia, to a bleeding in the mucosa. Möricke never noted any rupture of the vessel walls, and considered it probable, from the small size and arrangement of the extravasations, that the haemorrhage occurred by a process of diapedesis. He points out that all the previous authors had derived their material from patients who had been a shorter or longer period dead, and he declares that they have confused the post-mortem changes with the physiological. He found almost complete absence of the superficial/

superficial layers of the mucosa in two uteri removed from patients who had died during menstruation.

The investigations of de Sinety²⁹ led to results very similar to those of Moricke. He in addition, states that he found no cellular contents in the menstrual discharge.

³⁰
Wyder, in two papers, challenges the results of the two preceding authors. In describing two specimens removed four and eight days after menstruation respectively he notes more or less marked separation of the surface of the mucosa. He attributes it, not to a fatty degeneration, but to the bleeding. In the deeper layers of the mucosa there is present distinct cellular hyperplasia. The regeneration occurs from the remnants of the superficial epithelium and from the glands. Unlike de Sinety he noticed detached epithelial and stroma cells in the menstrual discharge.

(31)
V. Kahliden, using specimens obtained from patients who had died from acute peritonitis and acute febrile illnesses, says that during menstruation not only the superficial epithelium but also part of the blood-infiltrated superficial layer of the mucosa are detached. He states that whether the/

the bleeding is due to diapedesis or rupture is uncertain. The regeneration takes place exclusively from the gland cells.

Löhlein³², basing his conclusions on scrapings obtained from two healthy menstruating women, states that the bleeding is due to a process of diapedesis and that there is a separation of the superficial epithelial and stroma layers. Christ³³ endeavours to reconcile the divergent opinions by asserting that different healthy uteri show varying changes - in one there may be a wholesale destruction of tissue during the menstrual process, whilst in another there may be none. Jacobs³⁴ believes that the bleeding is due in part to rupture of some of the blood-vessels and in part to an escape through the intact walls of the capillaries. There is no detachment of mucosa.

Van Tussanbroek and Mendes de Leon³⁵ assert that in hyperplasia mucosa uteri bleeding into the tissues is found in no way differing from that found in menstruation. They make the interesting statement, moreover, that the loss of tissue is much more scanty in the case of the typical haemorrhages than in the case in menstruation. Here it is, however, not a sine qua non for the blood escape for they noted/

noted the blood corpuscles escaping between the intact cells of the surface epithelium. The next paper to demand notice is that of Heape³⁶ on the menstruation of the *Semnopithecus Entellus*. The facts discovered by Heape in regard to this subject are of so much importance in regard to their possible bearing on the process in the human female as to necessitate a somewhat liberal reference to his work. He divides the process into eight stages. The first is the resting stage. Stage 2 is the growth of the stroma. Here there is an increase of the stroma by amitotic division, which results in a swelling and increase in density of the upper third of the mucosa. Owing to pressure the nuclei become fusiform. There are no decidual cells. The vessels are distended. Stage 3 is associated with growth of the vessels. The mucosa is further swollen, the epithelium is stretched and is becoming thinner. There is hyperplasia of the vessels immediately under the stroma. In stage 4 there is breaking down of the vessels. There is first present hypertrophy of the uterine epithelium and the vessel-walls all over the mucosa; degeneration then sets in in the superficial regions with a breaking down of the capillaries and an extravasation into the tissues. The degeneration is not fatty,

fatty, but is probably amyloid or hyaline. There is no evidence of leucocytic emigration in the true sense nor of diapedesis of the red corpuscles. In stage 5 there is the formation of lacunae. Extravasated blood collects in lacunae, which are first formed more deeply in the stroma but soon spread to the surface, displacing the stroma elements till they reach the surface epithelium. There is no trace of blood escape in the deeper layers of the mucosa. In stage 6 there is rupture of the lacunae. They increase in size, the epithelium degenerates, shrivels up and is shed permitting of the blood escape. In stage 7 there is the formation of the menstrual clot, which is formed of the uterine surface epithelium, a portion of the glands, and the upper third of the stroma with the blood vessels and blood corpuscles. The process, he declares, is therefore, a severe, devastating periodic action, which is very remarkable. In stage 8 there is the recuperation of the lost tissue, the epithelium partly from the glands, and partly by means of a transformation of the stroma cells into a flattened epithelium. The new capillaries are formed from the "stroma cells which surround the intercellular spaces in which the extravasated blood lies, and in the return of this reclaimed blood/

lies, and in the return of this reclaimed blood to the circulatory system". The epithelium at first flattened assumes the usual cubical form.

³⁷
Wendeler makes the interesting statement that in some places previous to the shedding of the epithelium there is the formation of a fine epithelial layer under cover of the cells to be detached. Pompe van Meerdervoort,³⁸ using six uteri removed during menstruation describes a distension of the vessels and a serous infiltration of the tissues especially towards the surface. The surface and gland epithelium are swollen and dropsical. Just under the superficial epithelium there are extravasations, resulting from rupture of the vessels. At these places the epithelium is detached.

³⁹
Westphalen in 1896 published the results of the examination of scrapings from 50 women, in whom the exact date of the last menstruation had been noted. This material included also 12 uteri removed in the interval between two periods. He studied the nuclear changes especially and came to the following conclusions:- During menstruation and for the first six days counting from the day of the onset of the bleeding there is little evidence of mitosis in the cells of the stroma or epithelium. From the sixth to the eighteenth day numerous mitotic figures are evident/

evident in all the cellular structures - the stroma, the vessels, and the surface and gland epithelium. He never noticed an amitotic cell division as described by Heape in the *Semnopithecus Entellus*. From the eighteenth day till the end of the next menstruation the evidence of regeneration in the shape of mitotic figures disappears. About ten days before the menstrual flow there appears the premenstrual swelling, consisting of a serous and bloody infiltration of the stroma. The vessels are markedly distended before there is any evidence of bleeding. The glands also become widened, due to the accumulation of the secretion, containing leucocytes in greater or less quantity. The nuclei of the gland cells become more rounded. With the collapse of the mucosa towards the end of menstruation the epithelium and stroma, lifted up by the blow extravasations, sink down again; in general a short time after the period the mucosa is seen to be covered with an almost complete layer of epithelium and certainly before there is any evidence of regeneration in the shape of mitotic figures. There is doubtless a certain amount of epithelial shedding. There is present a certain amount of fatty degenerating of the cells in all the phases, a fact which tends to negative the conception that/

that on its occurrence the bleeding depends.

Gebhard in 1897 published the result of his researches on the condition of the mucosa during menstruation, deriving his material both from scrapings and uteri removed entire. He distinguishes three phases (1) The Premenstrual Congestion; through dilatation of the capillary vessels there is induced an oedematous exudation into the stroma, the meshes of which become enlarged, and the tissues are then infiltrated with blood. The blood is apt to collect in small blisters under the superficial epithelium, which is lifted off the underlying stroma - in this way the so-called subepithelial haematomata are formed. (2) The Blood Escape. The red corpuscles escape for the most part through the intact epithelial layer. Where the epithelium has been lifted up it again sinks down against the stroma with the escape of the blood. There may be a small amount of epithelial shedding but this is accidental. (3) The Postmenstrual Phase. The blood remaining in the tissues is absorbed for the most part: some, however, may persist for a longer time, becoming transformed into a brownish pigment. The cervical epithelium shares in the menstrual process only by furnishing an increased quantity of secretion.

Within/

Within the last decade only a comparatively few investigations into the histology of menstruation have been published. These, almost without exception, simply serve to substantiate the teaching of Mörcke⁹, de Sinety²⁹, Löhlein³², Gebhard⁴⁰ and others, that in the process there is little or no tissue destruction. Findley⁴¹ in describing several menstruating uteri removed by operation noted a limitation of the haemorrhage to the superficial layers and an almost complete absence of epithelial shedding. Whitridge Williams¹⁴, whilst agreeing with Mörcke that there is little or no destruction, believes that the haemorrhagic infiltration is more extensive.

Hitschmann and Adler⁴² have comparatively recently published investigations which, though not directly touching on the subject under discussion, have an interesting collateral bearing on the changes occurring in menstruation. They maintain that many of the cases of so-called endometritis glandularis are in reality not pathological states but merely correspond to the physiological glandular changes associated with the premenstrual state.

The correctness of this teaching is being tested. Some authors (Ellerbroek⁴³ and others) challenge its validity, whilst others (Norris and Keene⁴⁴, etc) incline in its favour.

CAUSE OF THE MUCOSA CHANGES IN MENSTRUATION.

As the investigations which I shall subsequently record would seem to come into close touch with the true nature of the agent or agents responsible for the uterine changes in menstruation, it will be necessary to refer in brief to this aspect of the literature.

From the middle of last century, with the work of Bischoff,¹⁸ Pouchet²⁰ and others, dates the conception that ovulation is of periodical occurrence and that between it and the changes which the uterine mucous membrane periodically undergoes in association with the menstrual process, there exists in some way an interdependence. In 1865 Pflüger¹⁹ as already mentioned, first definitely formulated a possible explanation of this relationship. The theory associated with his name supposed that the gradual enlargement of the Graafian follicle led to an increasing stimulation of the nerve fibrils imbedded in the ovary. When this stimulus attained a certain strength it led to the production of a powerful reflex dilatation/

dilatation of the vessels of the internal genitalia associated with the escape of the blood from the uterine mucosa. Although this theory of Pflüger has lost the support it used to command, the connection between the ovarian changes associated with ovulation and the mucosa changes in menstruation is still generally recognised by scientific workers. The demonstration by Leopold⁷, followed later by many other writers, that during menstruation there may be no evidence of ovulation in the ovaries proved conclusively that the two processes are not necessarily simultaneous and therefore, that ovulation cannot be considered as the immediate causal agent of the menstrual process. The well-known fact, moreover, that ovulation may occur in the absence of menstruation as proved by the occurrence of conception before the menarché and after the menopause, and during the amenorrhoea of lactation indicates if it does no more a still further independence of the two processes.

In 1871 Sigismund²⁶ advanced the idea that menstruation should rather be looked upon as an indication or rather as the result of the failure of conception. The changes which the uterine mucosa periodically exhibits were by him attributed to a preparation of a nest for the ovum and with a failure of conception/

conception the mucosa was separated, somewhat similarly to what occurs during abortion, with the production of the menstrual flow. As he stated "die menstruation ist mithin ein abortus". According to this theory ovulation precedes menstruation by some time and, in the case of pregnancy, the fertilised ovum corresponds to the ovulation period associated with the first monthly flow missed. Sigismund's theory received the support of Löwenhardt⁴⁵, Aveling⁴⁶, "Löwenthal"⁴⁷ and others. The more recent researches into the microscopic changes of the mucosa during menstruation, by demonstrating the absence of a shedding such as found during abortion, must be considered to cripple seriously, if not actually to invalidate this theory.

Although the existence of a relationship between the ovaries and the menstrual function had for long been foreshadowed by scientific workers it was not until comparatively recent times that this dependence was clearly and indisputably established. With the introduction of, and the extension of, the operative procedures on the genital tract, it has now been amply demonstrated that the removal of the ovaries is associated with an abolition of the menstrual function. In many cases after an apparently complete removal of the ovaries menstruation may continue/

continue and this, at first sight, might tend to controvert the above statement. The well demonstrated fact, however, that even the smallest portion of ovary left behind may suffice to retain the menstrual function would amply explain these apparently anomalous cases. The fact that, after the production of an artificial menopause by the removal of the ovaries, the uterus usually shrinks and atrophies (a statement amply borne out by recent experiments on animals) indicates that the ovaries exert in some way over the uterus a general trophic influence and are essential for its general nutrition. In the absence of this constant influence the atrophy which it undergoes leads to a falling into abeyance of its functions.

The exact nature of this influence still awaits solution, but by most workers now-a-days it is attributed to some secretion passed into the blood stream, by which not only the uterus but the general functions of the being are maintained at their proper level. This conception thus endows the ovary with a function apart from that of ovulation, and brings it into line with the ductless glands of the body (the islets of Langerhans in the pancreas, the/

the suprarenals, the thyroid, the pituitary, etc.)
⁴⁸
Fraenkel of recent times, developing and elaborating
 an idea which he attributes to Born, has suggested
 that this internal secretion, which is directly concerned with the changes in menstruation and pregnancy, is provided by the cells of the corpus luteum. In experiments conducted in animals he showed that if the corpus luteum be destroyed by the galvano-cautery immediately after the ovum is fertilised it does not enter the uterus. If destroyed soon after it has become engrafted it is shed. Destruction of the corpora lutea leads to a uterine atrophy. He thinks that the corpus luteum is necessary for the production of the hyperaemia of pregnancy. If the ovum does not develop the vascular changes result in the menstrual flow. The influence of the corpus luteum on the menstrual function is thus obvious. He tested these experimental results on patients in whom the abdomen had to be opened for some surgical complaint. In 9 the developing corpus luteum was destroyed. In 5 the menstrual flow was delayed beyond its expected time for periods varying from three to eight weeks. In three there was slight bleeding after the operation, such as is often met with after an abdominal operation, but the menstrual flow was delayed for eight/

eight weeks. In only one case was menstruation unaffected. This interesting theory is being widely tested, with results which seem on the whole to indicate the truth, at any rate, of some of its claims.

Two other theories advanced to explain the phenomena of menstruation must be mentioned to complete this summary. The first supposes that the flow is bound up with a periodical and rhythmic condition of the metabolic processes of a woman. This theory which was advanced in 1876 by Mary Jacobi,⁴⁹ associates the menstrual changes in some way with the apex of a wave of body changes, which reaches its maximum with the onset of menstruation, after which it sinks only to rise again before the next period. The second explanation of the phenomena is found in the so-called menstrual nerve theory. This attributes the changes to a special nerve in the ovary; This idea was advocated especially by Tait⁵⁰ and Johnstone.⁵¹ Neither of these theories received more than a passing toll of support.

INVESTIGATIONS ON THE MUCOSA DURING MENSTRUATION

MATERIAL. This consists of 3 specimens of the premenstrual mucosa. One is a specimen obtained post mortem in the case of a girl who was killed by an accident. The menstrual flow had just started but I have classed it under the above heading because it would/

would seem to correspond microscopically to the pre-menstrual rather than to the menstrual. It is well-preserved except for a shedding of the epithelium of the surface and the glands in the upper regions. The other 2 specimens were obtained by curettage

I have 1 specimen corresponding to the first day, one to the third day and 5 to the fourth day, of the flow. These and 2 specimens from the immediately post menstrual period (two days after) were all obtained by curettage.

From the summary of the literature concerned with the microscopic changes which the uterine mucous membrane undergoes during menstruation it will be evident that the opinions advanced are numerous and conflicting. With regard to the degree of disintegration present there are all grades of opinion from that of Williams,²⁷ who maintained that at each period there occurs a complete shedding of the mucosa, to the other writers Möricke,⁹ Gebhard,⁴⁰ de Sinéty,²⁹ Jacobs,³⁴ etc, who assert that there is usually no destruction of tissue. This controversy is to a large extent brought within smaller limits by the well-authenticated fact that during the agonal period and after death there may be extensive loosening and shedding of the mucous membrane, a condition which many/

many investigators would seem to have mistaken for a menstrual phenomenon. For, with few exceptions, the workers, who have limited their material to fresh specimens, in the form of scrapings of the mucosa removed by the curette, or in the shape of the whole uterus removed at operation, coincide in describing the tissue loss as small or absent. In this class are Leopold,⁷ Mörcke,⁹ de Sinéty,²⁹ Gebhard,⁴⁰ etc. From the observations of such investigators it would seem likely that during menstruation there is little or no loss of tissue.

My own specimens lend favour to this view. Here and there areas are present where two, three or more epithelial cells in a line are detached; for the most part, however, the epithelium on the surface and glands is well retained.

Figure 13 represents a common appearance presented by my specimens. The upper layers of the stroma are loosened and are infiltrated with blood and a serous exudate. At one region a portion of the epithelial layer is detached permitting an escape of red corpuscles and stroma cells into the cavity of the uterus. It will be noted that the loosening of the tissue is present all along the superficial part of the stroma - this would seem to be a/

a constant condition in the menstruating mucosa. Here and there in the substance of the stroma there are areas of extravasation; for the most part, however, this is confined to the more superficial parts of the mucosa. In some of the specimens the bleeding is completely absent except towards the very surface. In two of my specimens (representing the first day and the fourth day of the flow respectively) the degree of the haemorrhage into the mucosa corresponds to what has been described by many authors. Although the deeper part of the stroma is unaffected most of the superficial regions are the seat of a copious blood infiltration. In these respects my specimens differ from those of Möricke⁹ and others who maintain that the haemorrhage is invariably located in the surface parts. With regard to this point there is considerable discrepancy in the literature, some authors maintaining that the bleeding present is more extensive, others declaring that it is confined entirely to the upperlayers, whilst others are somewhat indefinite, and in cases a little careless, with regard to the conditions present. In this connection it is interesting to note that Whitridge Williams¹⁴ in his text-book of Obstetrics, whilst throwing in his lot with Möricke's description of the changes present, /

present, illustrates what he considers the typical condition with a figure in which the haemorrhagic infiltration is present to a considerable depth of the mucosa.

As in the extent of the blood infiltration of the tissues, the amount of the loosening present by the serous exudate would seem to vary within wide limits. Here again, however, the lower third of the mucosa would seem to be immune. In some of my specimens the opening of the tissue spaces involves only a very limited area at the surface of the mucous membrane, in other cases, and this is apparently the commoner condition, about the upper third of the stroma exhibits the changes, whilst in still other specimens an area comprehending the upper two thirds is seen to be teased out by the fluid exudate. According to Leopold, Gebhard and others this latter condition would coincide with the premenstrual phase of congestion and swelling, and, as a matter of fact, one of my specimens exhibiting this condition was derived from a patient in whom the menstrual flow had just set in. According to Leopold the escape of the blood is associated with the discharge of the fluid contained in the intercellular spaces. This results in a return of the previously opened out part of the stroma/

stroma to the more condensed condition associated with the resting stage. It seems likely that throughout the time of the menstrual flow the most superficial part of the stroma retains its opened-out, sponge-like nature. Such an interpretation of the changes would offer an explanation of the very varying degrees and extent of the serous exudate present, the mucosa exhibiting this condition in the most marked manner corresponding to a persistence of the premenstrual phase, which by gradations merges into the condition where only the very surface of the stroma is affected. The opening out of the upper layers of the stroma with a separation of the glands often widely from one another, while the deeper part remains dense, with the glands closely set together, often results in the differentiation of the mucous membrane into two parts resembling the upper compact, and the lower spongy layers of the decidua in pregnancy. (figure 14)

The serous exudation and blood extravasation into the superficial part of the stroma leads to a marked increase in thickness and in the surface area of the mucosa; this latter change is manifested by a folding of the mucosa. This surface undulation is probably most marked in the premenstrual phase (Leopold). How far the increase in tissue is due to

a multiplication of the stroma cells is doubtful - in none of my specimens is there definite evidence of this process at work and this observation, on the whole, would seem to conform with the more recent researches on the subject.

The finer microscopic details of the changes exhibited by the menstruating mucous membrane are best considered under two headings:-

(1) The alterations in the surface epithelium and the glands.

(2) The alterations in the blood-vessels and stroma. It is with these that we are more especially concerned.

ALTERATIONS IN THE SURFACE EPITHELIUM AND THE GLANDS.

As already mentioned it seems probable that during menstruation there is, under normal circumstances, little or no loss of epithelium. Where it occurs it is, as Gebhard states, accidental.

In the resting stage the epithelial cells covering the surface and lining the glands are closely packed together, the cytoplasm is finely granular/

granular and takes on a faint red stain with eosin, and the nuclei are usually distinctly oval and are situated towards the base of the cell. The free margin of the cells is provided with cilia.

During menstruation the epithelial cells become broader and it is often possible to detect tracts like vacuoles between the cells. One can frequently see red corpuscles lying between the cells at their bases though I have never actually been able to persuade myself of the existence of any conclusive evidence of the wholesale exodus of the red corpuscles between the cells. It would seem, however, that such must be the chief mode of the blood escape. It is frequently possible to recognise long, rod-like nuclei between the cells, corresponding apparently to leucocytes or stroma cells in the act of insinuating themselves to the surface.

There are usually evident changes in the nuclei in the epithelial cells during menstruation. They often swell up, they assume a more rounded contour, and they often leave the cell base and rise up towards the middle of the cell (Figure 5).

There is considerable divergence of opinion as to the manner in which the cilia are affected in the menstrual changes; some authors state that they are/

are seen to be well retained if care be taken in the preparation of the material, others state that they are represented by a homogeneous looking substance at the cell surfaces, whilst other writers state that they are lost altogether. My specimens lend support to the last idea, in most the ciliated margin has completely disappeared.

As already mentioned all along the surface of the mucosa immediately subjacent to the epithelium the stroma is loosened, the cells are detached from one another, and there is a general blood infiltration (Figure 13). This in some places leads to the complete separation of the epithelial cells from the stroma - in some regions the epithelium is elevated into sort of small blisters, in other parts the epithelium bridges across a space in the stroma without being lifted up. (fig. 16). These appearances constitute the so-called sub-epithelial haematomata of Gebhard.

REGENERATION OF THE EPITHELIUM.

It would seem that the consensus of opinion is in favour of the regeneration occurring, where there has been an accidental denudation, from the adjoining epithelium of the surface and glands. By some/

CHANGES IN THE BLOOD-VESSELS AND THE STROMA
DURING MENSTRUATION.

To appreciate the vascular and other changes which the mucosa exhibits during menstruation it is necessary to recall in brief the result of the investigations into the structure of the stroma and blood-vessels, which I have recorded in a previous part of this research.

It was pointed out that the stroma must be considered to be composed of a soft, multinucleated protoplasmic mass pervaded by a complex system of fluid spaces, which break it up into poorly differentiated cellular elements. The spaces lie up against the perinuclear portions of the protoplasm and separate the cells from one another except for bridging processes of the general protoplasmic mass (Plate I. and figures 1 & 4.). This description applies to every part of the mucosa. I have adduced evidence which tends to indicate that the fluid spaces in the ordinary resting state do not communicate freely with one another as is usually stated. It seems more likely that the bridges of protoplasm correspond to continuous films separating the adjacent fluid collections, which are thus contained in completely walled/

walled-in cavities or vacuoles. This conception will be further endorsed, and its importance will be revealed, in subsequent paragraphs. I have pointed out that the different cell forms detected in the stroma are not to be considered as indicating units differing in structure and function. The fact that these variations are easily dispelled during certain normal functional changes indicates that they are merely temporary in nature and are, in all probability, dependent on environmental conditions, especially extracellular pressure. This was seen to apply also to the basement membrane of the glands.

I have pointed out that the blood-vessels merely consist of tracks through this uniform stroma. It is probable that the vessels throughout the extent of the mucosa derive their supporting coats exclusively from the surrounding stroma elements, which are unaltered in the performance of their function except that where the blood-pressure within the vessels is greater they become more condensed round the lumen and in so doing often become drawn out tangentially to the vessel and arrange themselves in concentric layers (Figures 8 & 9). In the case of the arterioles the thicker the vessels (i.e. the nearer they are to the heart) the larger the number, and the greater the condensation/

condensation, of the surrounding stroma cells, whilst in the case of the capillary twigs the wall is represented merely by a single layer of flattened out stroma cells. The walls of the veins are constructed in a similar manner but are thinner than their corresponding arteries. These facts apply with equal force to the media and intima. This interpretation of the structure of the mucosa vessels is borne out to a considerable degree by the fact that into the composition of their walls there do not enter the differentiated structures found in vessels of a similar size in other regions of the body. In none of them, even the thickest, except in the very deepest portions of the stroma, is there ever present any muscular, fibrous, or elastic tissue. I have referred to the striking fact that, whereas the vessels in the muscular coat contain the ordinary muscular and elastic ingredients, these are lost almost immediately the stroma is reached. For some reason or other the vessels throw off their supporting coats in the mucosa, and I advanced the belief that such a structural arrangement must have its bearing on the changes in the vessels which occur in menstruation and pregnancy.

In/

In the premenstrual phase there is a marked swelling of the mucosa due, in the main, to distension of the blood-vessels, increased lymph escape, and blood extravasation. The latter is usually not marked except in the immediate proximity of the vessels. There is at the same time a marked softening of the mucous membrane; so manifest is this that the consistence becomes almost that of a jelly. This fact has been specially noted by several observers - Kundrat and Engelmann say that "the softening occurs to such a degree as to make the mucosa almost fluid in consistence". Leopold refers to the same condition, Mörcke states that the mucosa becomes "soft and pulp-like", and other observers bear testimony to the same effect. The slightest pressure is sufficient to injure the mucosa and it can be scraped with the greatest ease from the underlying muscle coat. It seems to me that this may explain to a large extent the wide discrepancy evident in the literature regarding the amount of damage present in the menstrual mucosa. In fact, in scrapings removed from the uterus during this period it is not uncommon to find the blood and stroma mixed up intimately with one another in an artificial way, indicating that the consistence of the two materials has been somewhat of the same/

same order. It can readily be understood how even gentle handling of a uterus in the operating theatre or the post-mortem room might be sufficient to damage the mucosa and thus lead to erroneous conclusions. These facts, combined with the well-known readiness with which disintegration ensues after death, afford ample explanation of the conflicting results obtained by different observers. As I shall immediately point out the softened, displaceable condition of the stroma is likewise of the greatest importance in determining the histological changes which occur during menstruation.

The oedematus opening out of the stroma during menstruation involves chiefly the upper strata and is absent, or only present to a small degree, in the part immediately adjacent to the muscle. The intercellular spaces become distended by the increased fluid escape, the protoplasmic bridges connecting the cells become drawn out and attenuated. In many cases they become completely detached and spaces of small or large size are produced in the stroma by a displacement of the cells. With the oedematous opening out of the tissue there occurs a marked alteration in the shape of the cells. They become rounded or stellate. In the oedematous stroma this is the only cell form present/

present (Plate I), with the exception of the leucocytes lying free in the spaces. We thus see that the changes associated with the menstrual function have led to the stroma cells becoming approximated to one type. The cellular distinctions become levelled - the oval and rod-like cells have disappeared and they have identified themselves with the general mass of poorly differentiated protoplasm. It was observations of this nature which led me to suggest the interpretation of the stroma, which I have previously formulated.

MODE OF THE BLOOD ESCAPE.

In the literature there is a considerable divergence of opinion regarding the exact manner in which the blood escapes from the vessels into the surrounding tissues during menstruation. Some observers consider that it occurs by a process of rupture with a subsequent discharge of the contained blood into the surrounding tissues, whilst others maintain that it occurs exclusively by a process of diapedesis or escape of the red corpuscles between the intimal cells, without an actual interference with the structural continuity of the vessel wall. Still other writers believe that both processes are at work.

My investigations, whilst convincing me that
in/

in the initial stages of the escape a process identical to that of diapedesis in other regions is found, have demonstrated that in the later stages of the blood exodus into the surrounding tissues a change of quite a different nature is present. It is dependent on the peculiar structure of the vessel walls, and whilst it is associated with a wholesale opening up of their component parts, it is fundamentally different from rupture as detected in other places in the body. In describing the results of my investigations it will conduce to clearness to consider first the fine-walled vessels, and then those with thicker walls.

BLOOD ESCAPE FROM FINE-WALLED VESSELS.

In many places in the premenstrual and the menstrual mucosa the red cells are seen to be leaking into the adjoining tissues between the lining cells of an apparently complete vessel wall. (Plate I and Figures 21.). In other cases the corpuscles have obviously detached the adjacent cells from one another (Plate I). It seems certain, however, that in both cases the same process is in operation, namely that the cells are passing out through gaps in the vessel boundary. In this respect, then, the escape coincides with the process of diapedesis. Before the occurrence/

occurrence of the corpuscular escape the surrounding tissues become opened out by the fluid exudate, in the manner described.(Plate I). After passing through the wall of an apparently complete vessel the red cells may stray for a considerable distance into the surrounding stroma. In so doing they may burrow along between the cells (Figures 18,19,20) or they may lead to a wholesale displacement of the surrounding stroma (Figure 23).

In addition to this simple change there is always found another, which, at first sight, is of a more complicated nature and one which, so far as I know, has never been properly described. This consists in the gradual expansion of the small blood lumen into a space of larger diameters, and which, especially towards the surface of the premenstrual and menstrual mucosa, results in the formation of the comparatively enormous blood lacunae or "distended capillaries" so typically found in this condition. The initial stage consists in a separation of the lining cells from one another. This, as we have noted, is preceded by a similar teasing apart of the surrounding stroma by the cedematous exudate. The spreading apart of the lining cells, at first only sufficient to permit the passage of the red cells, is followed by a complete detachment, the one from the other.

The/

The opening out of the adjacent stroma now enables these intimal cells to step back, and we then obtain a blood space apparently destitute of the ordinary flattened lining cells, for, in the process of separation, these are usually found, as it were, to draw themselves together and to identify themselves in every respect with the neighbouring stroma elements. In this we see a perfect analogy to the changes which I have described in the stroma cells when they are spread apart by a watery exudate. I have pointed out that under these conditions the cell distinctions disappear. The flattened cells of the basement membrane, and the elongated cells scattered through the stroma have lost their differential shape and are seen to resemble in every detail the typical round or stellate stroma element. So with the flattened intimal cell of the blood-vessel. In some places this vascular change is seen to involve one side of the wall, the other side retaining its usual flattened cells.

The various steps in the process are well brought out in figures 24, 25 . The changes are also brought out in Plate I , in a manner almost diagrammatic in its clearness. In the small vessel in the lower part of the plate the flattened appearance of the intimal cells is in parts well retained. That/

That this difference between these cells and the adjoining stroma cells is only present in one direction is demonstrated by the fact that where the wall has been cut across tangentially at their level they are seen to be indistinguishable from the stroma elements. Between the lining cells and the stroma cells are seen the same protoplasmic communications as are present between the ordinary tissue cells. At several regions the blood cells have strayed beyond the vessel confines and there the intimal cells have been carried outwards to range themselves alongside those of the stroma. In the other vessel, at the level of d, the same changes are present. The ordinary flattened cells have here been displaced outwards to a greater degree than is present in the other vessel. As is often noticed a few of them have apparently been left behind in the course of the expansion. This may be due partly to the fact that the intima is here cut across at a tangent. It does not however explain everything. I have repeatedly noticed that one or two cells may be completely left behind and remain as islands surrounded by the blood. They can usually be seen, however, to have retained a certain amount of protoplasmic connection with the adjoining cells. This change often progresses to the extent of forming large/

large blood sinuses in the mucosa, situated as already stated, for the most part, towards the surface. In this way are formed the sub-epithelial haematomata of Gebhard. The expanded vessel represented in Plate I is formed in such a way, and it indicates, what is often seen, that the expansion is still progressing. Here and there along its wall the blood is seen to be still escaping into the adjoining stroma, and the lining cells are still stepping back to allow of the increase in the diameters. A blood sinus similarly formed is represented on Plate II. Here as before the expansion is still seen to be progressing. This plate also indicates that, whilst round the greater part of the circumference the wall is formed by ordinary stroma cells, here and there flattened cells are present and identical in every respect with the intima of the resting vessel. Similarly produced blood sinuses are shown in figures.

As already pointed out, when the original intima is opened out the flattened appearance usually becomes dispelled and the newly formed blood space seems to be lined by ordinary stroma cells. An appreciation of the steps of the change enables us to understand the rationale of this. We now know that into the constitution of the new wall both the original/

original intimal cells and the adjoining stroma cells have entered, though in many cases it is impossible to tell which was which. As I have already contended this discovery is amenable to one explanation only, namely that the intima and the stroma cell are structurally and functionally identical. This idea is confirmed by finding that here and there round the wall of even a large sinus the cells are seen to be flattened like a true endothelium. This is seen on both walls of the large blood space figured in Plate II . If my interpretation of the mode of production of such a space be correct, these flattened cells correspond to stroma elements, which have assumed this shape.

These observations, also, enable us to understand the appearances which would seem to have perplexed other writers. In the literature one occasionally meets, in the course of an account of the mucosa vessels, with a description of vessels which are apparently formed throughout by the stroma elements. So far as I know it has never before been explained. In figure 28 are shown two vessels, one conforming with this description, the other with an ordinary flattened intima.

But, it may be urged, are these appearances not due to the fact that in the beginning the flattened/

flattened intima has been shed, allowing the stroma elements to come into direct contact with the contained blood? In answer to this I may state that I have never seen any evidence of this. On the other hand it is often possible to see the flattened cells being carried back into the stroma by the escaping blood. (Plate I at d & g). I have also pointed out that the stroma elements can assume a shape identical with that of the original intima, where they lie immediately against the blood (Plate II). That these appearances are not due to the fact that there has been a persistence and proliferation of the original intima cells is proved beyond doubt by the absence of any evidence of cell division.

It seems to me that the expansion of the originally small vessel into a sinus-like space is due entirely to a process of displacement. It is initiated by a teasing apart of the intimal cells followed by a giving way of the surrounding stroma. In its final form the new wall is formed almost entirely of the stroma elements.

The structural peculiarity of the stroma has now amply justified its existence. The fact that it is composed of a soft, homogeneous protoplasmic mass allows of the occurrence of the above functional/

functional changes with the greatest possible efficiency. The vascular expansion is no more by a process of rupture than is the displacement produced in a mass of jelly by forcing into it a firmer body.

The probable explanation of the cause of these changes and their bearing on the mode of formation of the blood cavities in the pregnant mucosa will be discussed in subsequent sections.

CHANGES IN THE THICKER-WALLED VESSELS.

Where the vessel wall is supported by a massing of the stroma cells in concentric layers round the intima the blood escape is naturally resisted to a greater extent than in the case of the capillary twigs. Here, however, exactly the same teasing asunder of the surrounding cells by the fluid exudate followed by an escape of the corpuscular elements is always seen in the menstrual mucosa. After the opening out of the adjacent stroma the circularly disposed media cells are allowed to become stripped off. In the case of the thicker vessels this must, of course, first involve the outer structures, the remaining cells then becoming teased out in successive layers from without inwards. This change sometimes/

sometimes involves the wall uniformly round the entire circumference, in other cases one aspect gives way before the other. In many cases it is possible to see the detachment of the cells in complete layers, which, if the cells are united together by uninterrupted films, must correspond to complete protoplasmic sheets (Figure 17). The appearances associated with these vascular changes are well brought out in Figures 9,30,31.

With the completion of the detachment of the supporting elements the intimal cells become separated, permitting an escape of the corpuscular elements of the blood. The process now corresponds in every respect to that described above in connection with the capillary vessels. The blood strays out between the lining cells of an apparently complete wall, or in the process these cells are carried outwards and, with the surrounding stroma, become increasingly displaced to form the wall of a new blood sinus or lacuna.

In figure 29 is represented an appearance frequently detected in the menstrual mucosa. Towards the left side the vessel wall is well supported. On the right side there is seen to be a wholesale escape of the red cells into the surrounding stroma/

stroma. There has obviously been an expansion of this part of the vessel lumen, resulting in a carrying out of the intimal cells along side the stroma elements, from which they are indistinguishable. This figure indicates that in the blood escape there may be no definitely marked stages in the opening out of the wall: the intima and stroma become uniformly displaced outwards.

These changes which we have just described in connection with the thicker vessels again prove beyond doubt the easily displaceable nature of the structures and they, in addition, confirm in the strongest possible manner the description I have advanced of the true nature of the stroma. Blood vessels and surrounding tissue are simply part and parcel of the same soft nucleated protoplasmic mass. This structural peculiarity of the mucosa is obviously designed for the purpose of permitting with the greatest possible efficiency an immediate flushing of any part of the stroma with a plentiful supply of blood. If we are to define the true nature of the mucosa in terms of the functional changes which it exhibits it must be designated, not merely a spread out lymph surface such as Leopold named it, but a potential blood sponge. In view of these observations we can now appreciate fully the reason and the/

the necessity of the vascular structure - the presence of any fibrous or elastic tissue in the wall would obviously hamper the occurrence of the ready opening up which I have described.

The displaceable nature of the stroma tissue, in addition, is obviously devised for the purpose of allowing the ready formation of the blood sinuses which develop in the menstrual mucosa. Prima facie it would seem not unlikely that the blood lacunae, which correspond in conformation to these described, though often reaching a much larger size, that are found in connection with the chief functional activity of the mucosa (pregnancy) would owe their origin to changes similar to these just described. This I shall refer to in a subsequent section, and there I shall also adduce evidence in support of the idea that the ovum bed is for the most part, formed by a similar process of displacement and not by a process of destructive excavation.

CAUSE OF THE BLOOD ESCAPE DURING MENSTRUATION.

Most investigators have inclined to the idea that the escape of the blood from the vessels is to be attributed to a congestive process, in a manner somewhat similar to that first enunciated by Pflüger. This conception runs through practically all the more recent contributions to the literature, though it would seem that there is a tendency to abandon the explanation originally advanced by Pflüger that the vascular engorgement is induced by a reflex nervous stimulus from the ovary, the tissues of which become pressed upon and irritated in the process of the growth of the Graafian Follicle associated with ovulation. Though it still awaits confirmation there is a distinct leaning to the idea that the changes are dependent on some substance of a chemical nature, probably derived in some way or other from ovary (Fraenkel). The older writers (Williams, Kundrat and Engelmann, and others) saw the immediate cause in a degenerative change of a fatty nature in the mucosa resulting in a mechanical giving way of the vessel walls. Leopold, Möricke, Wyder, Heape and others, however, have indisputably proved that this fatty change, /

change, except in abnormal circumstances, is either absent altogether or is present only in a minor degree, and they have denied that it can in any way be considered as the causal agent. This has been amply confirmed by recent research, and it would seem that, where present, the fatty change must be looked on as due to the illness from which the patient died, from post-mortem change, or to the effects of the superficial destruction of tissue the result of the bleeding.

From what has been said on previous pages it will be understood that the exodus of the red cells through the vessel precincts is intimately associated with the oedematous escape from the vessels. The corpuscular exit occurs only after the opening out of the cells of the media and the production of gaps

in the intima of sufficient size to accommodate the red cells, in other words, that the process occurs only after the preliminary infiltration and loosening of the stroma protoplasm by means of the serous exudate. As I have pointed out in several places, the converse of this statement is untrue, namely that an oedematous infiltration is necessarily associated with a blood escape into the affected tissue./

tissue. One not infrequently finds an extreme watery loosening of the stroma without an escape of the red cells, and even where the lining cells of the vessel are seemingly so opened apart as to accommodate between them one or more red cells. Under these circumstances the vessels are often seen to be engorged with the red corpuscles which may actually lie right up against the vessel boundary. This I have shown to occur even when the vessel wall is formed clearly by the ordinary stroma elements, and I have adduced from this that the cells are not as usually stated merely united by protoplasmic fibrils but that, under ordinary circumstances, they are connected by complete, though thin, films of protoplasm, the giving-way of which is essential for the leakage of the red cells. The preceding watery escape has occurred through this fine sheet, in a manner to be presently described.

The fact that the escape of the fluid constituent of the blood precedes and, in fact, prepares the way for, the subsequent corpuscular exodus indicates that any investigation which casts light on the former process will go far to elucidate the problems associated with the latter.

FACTORS/

FACTORS DETERMINING THE FLUID ESCAPE
FROM THE VESSELS.

In conducting an enquiry into the etiological factors responsible for an increased transference from vessel lumen to tissue spaces in the uterus we are brought up against many investigations of a similar nature which have been carried out by other observers for the purpose of elucidating the agents which determine an oedematous escape in other regions. These investigations have been for the most part experimental in nature and, in most cases, have been carried out on the assumption that the changes, which determine the increased fluid escape, that constitutes oedema, are similar in nature with the physiological changes that ordinarily dominate the process of lymph formation. In the case of oedema these factors have remained the same, but they have become altered in the direction of an increase. With these possible factors must be included any condition leading to an obstruction of the normal lymph flow. This, it is obvious, may lead to an accumulation in the tissues of lymph, which though normally produced, collects in excessive amount. The justification of thus arguing from/

from the one condition to the other is seen to be complete when we remember that in the former enquiry all the possible factors responsible for the fluid transference must be included.

As I have considered it wise to enter in full into the discussion of the exact mode of production of an oedematous escape in connection with the changes detected in the pregnant tube, I shall refer to it here only in so far as is necessary to explain the histological changes revealed in my specimens of the menstruating mucosa.

In the first place it is easy to dispose of the last of the factors enumerated above, namely a lymphatic obstruction, as the direct cause of the fluid accumulation in the tissues. The justice of this will become evident in the course of this record. Suffice it for the moment to state that in the changes I believe we have sufficient evidence to prove beyond doubt that there is some process leading to an increased escape from vessel to tissue.

What are the factors that may determine the flow of fluid from vessel to tissue? It would seem clear that these must be comprised within (1) changes in the blood or the blood-pressure, and (2) changes in the vessel wall or the tissues. In regard to the relative/

relative importance of these different factors there is a considerable divergence of opinion amongst physiologists and pathologists. This difference of opinion is seen in the varying theories advanced.

(1). In the first place the so-called Physical Theory explains the fluid transference as due to purely physical processes. This may be due merely to a filtration through the wall from the vessel, where the fluid pressure is higher, to the tissue, where it is lower. This was originally advanced by Ludwig⁵² as a complete explanation of the phenomena. All recent workers on the subject, whilst admitting that this squeezing of the fluid through the wall may explain the phenomena in part, are convinced that in addition we must assume the existence of the processes of diffusion and osmosis, called into play by tissue changes which result in the formation of crystalloidal substances. Here again the exact status of these processes is still indefinitely defined. The great uncertainty associated up to the present with the study of the fluid transference under normal and pathological conditions is due, in the main, to the difficulties encountered in the experimental investigations and the correct reading backwards from the effects on the amount of the lymph flow of artificially varying circumstances to the factors which cause/

cause these variations, and thence to the agents concerned in the normal lymph escape and those acting in disease. Besides these processes of filtration, diffusion, and osmosis, Starling,⁵³ in order to explain the variations seen in different regions of the body, has suggested an additional factor in the shape of an altered permeability of the endothelial lining.

(2). The Second or "Vital Theory" of Heidenhain⁵⁴ and his supporters supposes the fluid transference to depend on a secretory activity of the endothelial cells.

In describing the results of my investigations into the changes responsible for the increased fluid accumulation in the premenstrual and the menstrual mucosa, I shall describe, in the first place, the process as demonstrated in the case of abnormally thick vessels, and, in the second place, as it is manifested in the normal vessels and stroma. This plan I intend to adopt merely for the sake of greater lucidity. As I shall subsequently indicate the actual changes are often obscured beyond recognition in the case of the normal mucosa. This fact I believe to explain the frank admission by many observers of their inability to correctly decipher the factors in operation. In the case of abnormally thickened vessels, /

vessels, whose walls, as it were, resist the fluid escape, the changes, on the other hand, are more easily traced. For this reason and in view of the fact that this research, I believe, breaks new ground, I have thought it wise to commence with the obvious and thence to pass to the less clear.

MODE OF PRODUCTION OF OEDEMA AS SEEN WITH THICK-WALLED VESSELS.

The observations to be recorded were carried out in a menstruating uterus removed by vaginal hysterectomy, from a patient of 42, who had suffered from severe and protracted menstrual periods for many years. Every form of treatment, including curettage, had been tried without avail. The usual course in these cases was adopted and the uterus was removed. This was done on the eighth day of a protracted period. After removal the specimen was almost immediately plunged into Pick's Solution (No 1) for hardening.

In the stroma, and as I shall show in the next section, in the vessels, changes of a nature similar to those present in the ordinary menstrual mucosa were seen. The mucous membrane was markedly thickened and softened, these changes extending throughout/

throughout the entire extent of the uterine body. The microscopic alterations in structure are similar in nature, though in an exaggerated degree, to those seen in the normal menstruating mucous membrane. The superficial part of the stroma, especially, is markedly oedematous and is infiltrated with blood. With the exception of a shedding of the superficial epithelium in parts there is no evidence of tissue destruction. The glands are markedly dilated, in some places forming cyst-like dilatations in their course. (Figure 36).

THE VASCULAR CHANGES.

These are of especial importance from the point of view of our present enquiry. The blood escape from the vessels is found to have occurred exactly as described in the preceding section with regard to the processes at work in normal menstruation. There is the same teasing out of the stroma and the vessel walls by an oedematous escape followed by a wholesale exodus of the red cells. Here again the change is most evident towards the surface.

Throughout/

Throughout the stroma, even towards the surface, a large number of vessels are seen with walls thicker and more condensed than are ever found in the normal mucosa (Figures 36, 37, &c). It is in these vessels especially that we find important information regarding the mode in which the oedematous escape has occurred in this abnormal specimen.

The unusual thickness of the vessel coats is due to a marked condensation of the surrounding stroma. Immediately external to the intima the cells are closely packed together, forming a deeply staining mass rich in nuclei. The stroma external to this is often arranged in concentric layers round the vessel (Figures 38, 46). We thus see that the great difference between these vessels and those of the healthy mucosa is found in the packing together of the cells to form the pathological media. As I shall point out this is not to be considered as, in any way, analogous to the media of similarly thick vessels in other organs. For under certain circumstances the cells can open up just as I have described in the normal vessels and we then see that they apparently correspond in every detail to stroma cells.

In many of these vessels I have been able to note changes which throw important light on the exact/

exact mode in which the oedematous escape, which has ploughed up the surrounding tissues, is taking place. In Figures 37, 40, & 44. are represented vessels whose walls are teased out by fluid tracks that extend into the adjacent tissues where they usually expand into large clear territories because of the more easily displaceable nature of the stroma. In Figure 44 this appearance is shown; the remarkable change present is due to a wholesale gap in the outer, less supported portion of the vascular wall, which gives the impression that it had been forcibly excavated. In Figures 37, & 40, the same condition is present and here the adjacent tissue is seen to be drawn out and to radiate from the vessel wall in the direction of the escaping fluid. These conditions are obviously due to the fact that the thick vessel walls have resisted the oedematous outpouring except in certain regions where they are less firmly knit together. At first sight the giving-way would seem to be readily explained by mechanical means i.e. increased intravascular pressure resulting in a filtration of fluid through the vessel wall with a displacement of the surrounding unsupported stroma and then of the outer layers of the vessel. Whatever be the cause it is clear that, to induce the marked displacement evident in many of/

of the vessels (vide especially figures 37 & 44), it must correspond to a comparatively great pressure.

A careful scrutiny of the histological appearances present demonstrates with certainty that the fluid cannot be escaping from the vessels in response to merely mechanical influences. There is some influence of a more complex nature than a mere squeezing or filtration from the blood vessel into the tissues. In the first place, in many cases it is possible to detect that, separating the vessel lumen from the oedematous track ploughing up the wall, there is nothing but a very fine, though complete, pellicle of cell protoplasm (Figures 37&46). It seems to me that a mechanical force sufficient to detach the cells of the markedly condensed wall in the wholesale manner in which the process is obviously occurring would result in an immediate rupture of the very attenuated protoplasmic bridge to which I have referred. It would seem absolutely certain from the appearances that the hydrostatic pressure on the immediately outer aspect of the pellicle must be, at any rate, not appreciably lower than that in the vessel lumen. If this actually were the case nothing could save it from immediate rupture. This appearance is often present and indicates that to explain the phenomena we/

we have to invoke some influence other than a mere mechanical transudation of fluid.

Another fact of the greatest importance is found in the observation that the fluid in the immediately adjacent portion of the vessel wall has accumulated under a hydrostatic pressure actually higher than that present in the vessel lumen. This is clearly indicated by the appearances present in the majority of the vessels. In figure 45 which is a drawing under higher magnification of the lower part of the vessel represented in figure 37, it is seen that on the left side the collection of the fluid in the inner part of the vessel wall has actually resulted in a bulging of the affected portion into the cavity. The fluid spaces in and between the cells have swollen the corresponding region inwards. On the right side of the same vessel at its lower part the same condition is present. Above this it is again seen and here it has been associated with a more profuse fluid exodus into the adjoining tissue, which in the process has been extensively teased out.

From what I have said above it will be obvious that at the regions corresponding to the protoplasmic film represented as figures 37 & 46, any marked discrepancy between the pressures on each side would/

would immediately cause a giving way. We have seen that in view of these facts a mechanical influence fails to account for the appearances. It will be left for us to deal with this same difficulty in the subsequent paragraphs. It seems to me that these observations prove beyond doubt that the fluid which is leaking through the vessel wall is entering the tissues under the influence of some force other than a mere mechanical filtration from vessel lumen. If such is the case, what other factors can be called in to explain the phenomena? A reference to the formula comprising all the possible agents which I have inserted at the beginning of this discussion discloses the fact that we are left in our search to changes in the intimal cells of an active secretory nature and changes in the tissues as a whole.

THE RÔLE OF THE INTIMAL CELLS.

In practically all the thick-walled vessels exhibiting the oedematous opening out of their walls there are present remarkable and important alterations in the intimal cells, alterations which might, at first sight, suggest that the fluid transmission from vessel to tissue is occurring by a process of vital or secretory/

secretory activity as opposed to a process of a physical diffusion or osmosis, which as we have noted completes the list of the possible responsible agents. At the outset I would submit that it seems unlikely that a secretory activity, whatever this may mean in terms of physical and chemical cellular changes, on the part of the lining cells would of itself suffice to explain the drastic vascular and tissue displacement present. I would advance as logical the opinion that an active change of such a nature cannot account for the wholesale opening up of the thick and dense vessel wall and the adjacent tissues external to the intima, and in support of this I would call attention to an appearance already advanced as contra-indicative of a purely mechanical or filtration explanation. A glance at figure 46 shows that the fluid track on the right side of the vessel wall is broken by fine tissue bridges or films; it seems to me likely that an active passage of fluid across the intimal layer so powerful as to tease out the wall to the degree present would inevitably break down the fine tissue partitions interposed in its path. On the other hand, the persistence of these very films, I shall indicate in the ensuing paragraphs, is amply accounted for and, in fact, is only explained by, the introduction/

introduction of a factor other than a filtration or a local intimal activity. Their presence is more than a coincidence - it is intimately bound up with the tissue changes which dominate the whole process.

In Figures 40, 41, 43, 45 & 46 are shown the changes in the intimal layer to which I have referred. The cells have been markedly swollen and projected into the vessel lumen by the collection in their substance of a clear fluid. In some instances the appearance somewhat suggests that associated with an intracellular fatty degeneration. That it is not so is at once proved by preparing and staining the sections in the appropriate manner. The changes are without doubt due to an accumulation within the cells of fluid abstracted from the vessel lumen and which has collected in the cells under a hydrostatic tension in excess of that present in the blood channel. It must be dependent on some protoplasmic alteration leading to an active fluid imbibition. Although with regard to the exact nature of the chemical changes involved in such a cellular alteration, which has been frequently noted in other regions of the body, scientific workers are still in ignorance, on some aspects of the subject there is a unanimity. Whilst the secret of the inner changes still awaits elucidation, we are/

are enabled, thanks to experimental research, to account for the results in a manner which leaves little room for uncertainty. According to Adami⁵⁵ "this rapid imbibition and accumulation of a fluid in a cell can, upon physical grounds, have only one explanation. The constitution of cytoplasmic matter, as also of the nucleus, is colloidal, and colloidal membranes (for such we can regard the surface layers of cells) have characteristic properties. They hinder the diffusion of crystalloid molecules to a considerable extent". The hydropic accumulation is due to some protoplasmic change associated with the liberation of crystalloidal elements. These raise the osmotic tension of the cell and this results in a diffusion across the cell membrane from the vessel till the osmotic pressures on both sides of the membrane are equal. In this way, and in this way only, can we explain the vacuolar changes in the intimal cells, which are, as the figures show, associated with a displacement of the nucleus and cell substance to the periphery by the accumulating fluid. In many instances the swollen cells project like blebs, often massed together, into the vessel, whose lumen may be distinctly encroached upon in the process. (Figures 45,&47). In other cases the swollen cells stand out as/

as elongated bodies or as isolated beads set into the inner vessel wall, (Figure 43). These appearances thus demonstrate beyond doubt that all along the inner aspect of the vessel walls there are present cellular changes which have determined an active imbibition of fluid from the blood.

THE ROLE OF THE STROMA PROTOPLASM.

What bearing have these observations on the mode of production of the diffuse oedematous infiltration of the surrounding vessel walls and stroma? If the opinions I have advanced in a preceding section of this research be correct, that in the uterine stroma we have a collection of poorly differentiated cells, all of which, intimal as well as ordinary stroma cell, are structurally, and, apart from the accident of location, functionally identical, it would seem not unlikely that in the above changes we are getting near an explanation of the diffuse fluid escape. Whatever be the original cause of the changes in the intima, it would seem likely that this cause will act similarly on the cells of the vessel wall and the adjacent stroma, and that, in this way, there would be set into action diffuse tissue changes culminating in a widespread absorption of fluid from the blood-vessels. If we can discover changes in the stroma/

stroma elements similar to those detected in the intima, not only do we advance far in connection with our quest, but we are able to indicate that the intimal alterations are to be considered more as an incident in, than as a cause of, the increased fluid escape, in other words, that there is nothing to favour the recognition of a local secretory activity on the part of the lining cells.

The changes present in the vascular walls and in the stroma strongly suggest that in these regions the oedematous accumulation has occurred in consequence of tissue changes identical to those evident in the intimal layer. The situation of the cells in the latter situation has, of course, forced the process at work into prominence and has thus enabled it to be deciphered with comparative ease. In Figure 46 it will be noted that, on the right side of the vessel wall, the fluid accumulation is associated with tissue changes identical with that present in the immediately internal lining cell. As in the case of the intima the fluid has collected in distinct vacuoles in the cell protoplasm, which has been displaced to the periphery as a fine layer, separating the one fluid space from that in the immediate neighbourhood. It is seen that the fluid track is for this reason not complete but is interrupted by a number of these fine films./

films. This appearance, as I have pointed out, is amenable neither to a mechanical explanation of the fluid exit nor to a local activity of the intimal cells. In neither case is it likely that there could be produced the drastic changes which I have described, and if it were possible to explain the gapings by either of these two processes it is inconceivable that the powerful Kinetic force thus acting could be resisted by the fine protoplasmic bridges. If both of these explanations fail we are again left to tissue alterations which have determined an osmotic diffusion of the fluid into the opened out regions. I would submit then that to explain the oedematous accumulation in the vessel wall, as in the intimal cells, we have perforce to recognise the existence of protoplasmic changes associated with the liberation of crystalloidal elements. This results in an increase in the osmotic tension of the tissues with a diffusion of fluid from one region to another across the colloidal membranes furnished by the tissue films. These retain the crystalloidal elements in the tissue. The diffusion stream in an outward direction will continue until the osmotic tensions on either side of the membranes are equal.

To understand the manner in which the tissue changes present result in a continual stream through the/

the vessel wall into the stroma, leading to the ploughing up present, it is only necessary to appreciate the manner in which the fluid escapes from the intimal layer into the immediately external tissue. As already stated the fluid enters the intimal cell in an endeavour to readjust the osmotic discrepancy between the protoplasm and the blood. From this it would seem clear that the imbibition of the fluid results in a lowering of the osmotic tension of the lining cell. This establishes a discrepancy between it and the immediately external protoplasm with a diffusion of the fluid outwards. The fluid which it thus loses it must again imbibe from the blood vessel. It is clear that these changes advancing in an outward direction will determine, so long as there are tissue bridges present, a continual stream of fluid. The fact that in the inner portion of the vessel wall, at any rate, changes such as I have described are occurring is proved beyond doubt by the fact that with an opening out of the vessel wall the swollen intimal cells in the corresponding region are invariably seen to collapse. (Figures 45,47). The most markedly distended cells are almost always in vessels which exhibit the teasing out in the least degree. These facts indicate that the fluid imbibition of the cells is/

is to be taken as a clear sign of the existence of such osmotic changes. They also explain the influence of the condensation of the vascular walls in determining the intimal changes, and conversely why in the finer vessels with easily opened out walls the process is apt to be completely obscured.

In view of the above-recorded facts it is easy to understand why in the dense vessel walls the fluid spaces are small whilst they enlarge as the stroma is reached. In the light of these facts, also, we can understand the expansion of the inter-cellular spaces. The fluid entering each of these is being drawn in by osmotic diffusion and we can now readily understand the rationale of the structure of the spaces. The fact that they seem to be not freely communicating but each separate and bounded by a complete protoplasmic film means that each space with its surrounding protoplasmic wall constitutes a perfect osmotic machine. The soft displaceable nature of this fine wall permits of its easy giving way permitting of the gradual expansion of the fluid tracks, till in some cases they reach enormous dimensions. In the next section I shall amplify what I have already said regarding this remarkable conformation of the uterine stroma and there I shall adduce evidence in proof of the fact that the soft, semi-fluid protoplasm/

protoplasm is to be considered not merely as a material devised for an easy mechanical giving-way but as an arrangement by which every portion can, in response to osmotic changes, become immediately supplied with the blood fluid. In this connection it will be seen that the so-called intricate network described by many writers in the stroma is in reality due to the appearance in the protoplasm of fluid vacuoles formed in the above manner. The variability of this "network", which sometimes is simple (Figure I), in other cases exceedingly complex (Plate III), to which many writers have referred, is to be looked upon, not as a mere coincidence, but as an indication of the perfect manner in which the stroma protoplasm is adapted for its many and varying functional changes.

MODE OF ESCAPE OF RED BLOOD CORPUSCLES.

Whilst the fluid constituents of the blood have been seen to be escaping by a process of diffusion across complete protoplasmic films, for an escape of the more solid corpuscles it would seem certain that there must be a corresponding giving-way of the tissue bridges. In all the vessels in this specimen from which the blood corpuscles are escaping the exodus is only/

only occurring at that part of the wall, which is completely opened from intima to stroma (Figure 47). In the case of the fine vessels this is easy and there is accordingly an extensive capillary haemorrhage going on in a way exactly like what occurs in the normal menstruating mucosa.

What factors determine the corpuscular escape from the opened-out vessel? In view of what I have said it would seem certain that the continual fluid stream from vessel lumen to stroma in the manner described must carry out the corpuscles into the stroma as far as there is a complete continuity of the track. As the osmotic stream of fluid must be in force not inconsiderable, this of itself would seem amply to account for the haemorrhage, although it must be remembered that subsequent to the opening out of the wall the ordinary intravascular blood pressure may take a share in the changes. The intravascular blood pressure dependent on the vis a tergo must, as the result of the continual dragging forward of the fluid by the tissues, in these conditions be considerably supplemented.

The manner in which the fluid and corpuscles are conveyed to the uterine cavity will be touched on in the next section.

CAUSATION/

CAUSATION OF EXCESSIVE UTERINE HAEMORRHAGE
AS REVEALED IN THIS SPECIMEN.

Before passing on to discuss the cause of the oedematous and blood escape in the normal menstrual mucosa a few words must be said regarding the light which the above observations throw on the obscure problem of menorrhagia. In the next section I hope to indicate that the cause of the oedema and haemorrhage in the normal mucosa is due to factors identical in nature with, and differing only in the degree of their activity from, those operating in this abnormal specimen. If this be the case it would contribute additional support to the widely entertained idea that in many cases of menorrhagia, and probably also of metrorrhagia, we are dealing with an abnormal activity of the ovarian influence.

Apart from the similarity of the tissue changes present in the two conditions which I mention here in anticipation for the purpose of completing this section, there are other considerations which render it improbable that, in the excessive bleeding in the mucosa in the case just described, we are dealing with an influence fundamentally different from that/

that normally acting. In the first place the bleeding merely consists in an increase in the quantity of the menstrual loss, and an extension of the duration of the menstrual flow. This would suggest that the same factor is operating, modified either in the direction of an increased activity or by some uterine changes which render the tissues more susceptible to its action. Which of these two different factors is responsible for the pathological haemorrhage it is impossible to say with certainty. It would seem unlikely that it can be due merely to the vascular thickening, for we have seen that, so far from increasing the tendency to the oedematous and blood escape, this change has actually tended to prevent their occurrence. In view of this it would seem to me that we are entitled to assume either that the vascular thickening is a coincidence or what is much more probable, that it is the result of the influence responsible for the other pathological conditions i.e. excessive oedema, bleeding, and glandular distension. If this is so it would seem not unlikely that in this specimen we see the results of an excessive activity of the influence which normally is associated with the four or five days moderate flow of blood from the uterus.

MODE OF FLUID ESCAPE IN NORMAL
MENSTRUATING MUCOSA.

I have repeatedly referred to the fact that the vessel walls in the normal mucosa are so formed as to allow of an easy and immediate opening-up of their structures by the oedematous exudate which precedes the corpuscular escape. In the last section I have shown how the abnormal condensation of the stroma forming the wall has forced into prominence the exact manner in which the fluid is being passed out. We have there seen that the tissues are actively dragging out the fluid and are not merely playing a passive rôle such as all previously advanced explanations demand. I have also shown how, immediately after the fluid exodus culminates in a free gaping of the vessel wall, the signs of this active tissue change are apt to become obscured at any rate on the inner aspect of the vessel. It is thus obvious that if the same process is being enacted in the normal stroma the peculiar/

peculiar structural arrangements present here will tend to veil the exact stages of the change. And this I believe explains why the real nature of the process has hitherto evaded detection. When the intercellular spaces become enlarged and the cells are widely separated it is often difficult to determine that this has occurred in any way but by a mechanical leakage of fluid into the tissues.

A careful scrutiny of the structural changes in the vessels and stroma associated with the menstrual condition has, however, convinced me that exactly the same process is operating as in the last case, that the fluid exudate and therefore also the haemorrhagic escape are taking place not by a mechanical squeezing of the blood from vessel to tissue, but that the fundamental cause is to be found in alterations that determine an active fluid imbibition by the tissues of the vessel wall and stroma.

On Plate V. is represented an accurate representation of an appearance frequently detected in the menstruating and the premenstrual mucosa. The specimen from which this drawing was made corresponds to the premenstrual condition. It will be noted that there is a marked oedematous opening out of/

of the tissues. This has been followed by the escape of two red cells into the region immediately external to the vessel lumen. They are lying in a clear space in the stroma. The appearance that I wish particularly to call attention to is the extra-ordinary tissue change associated with the fluid escape. The typical appearance of the stroma in the shape of more or less well formed cells united by comparatively simple protoplasmic processes (Figures 1, 3, & 4.) has become completely modified. Instead of the comparatively small number of large fluid spaces the protoplasm is beset with a multitude of spaces which in some cases are so infinitely small as to be just recognisable with this high magnification (X 1000) whilst in other places they attain dimensions as large as, or larger than, the ordinary intercellular space. The same changes are present in Plates IV&VI. It will be noted that the change has involved the protoplasm uniformly throughout its entire extent - it has obviously led to a breaking up of the comparatively thick protoplasmic communications, which in the resting mucosa pass between the cells, into the fine fluid spaces separated by the greatly attenuated cytoplasmic walls. It has also involved the perinuclear cell protoplasm often to a like degree - the usual mass of cell substance enclosing the/

the nucleus is often completely replaced by an infinite number of fluid spaces each bounded by the displaced and finely drawn-out cytoplasm of the original cell body. In Figures 26 & 27, I have represented the changes which the cells often exhibit in the oedematous stroma as contrasted with the simple protoplasmic arrangement of the resting state. It is clear that the formation of the fluid spaces in the cell body and in the connecting protoplasm is associated with a marked increase in the bulk of the affected tissues.

The appearances thus revealed are clearly amenable to one explanation and to one explanation only. They must be due to alterations in the cytoplasmic composition leading to an active fluid imbibition. A mechanical increase in pressure in the intercellular space might lead to a wholesale displacement of the cell body or of the intercommunicating cytoplasmic connections, but it could never induce the changes described. They can be attributed only to a chemical alteration associated with the liberation of crystalloidal elements and an osmotic diffusion across the protoplasmic colloidal membranes. Each of the spaces corresponds to fluid thus actively imbibed. While the exact nature of the chemical alterations/

alterations is still beyond our grasp we are left in no doubt regarding the results they produce. I have already described changes of a similar kind in connection with the menorrhagic mucosa and whilst, in the last section I intentionally devoted more attention to the changes located in the vessel wall, I may state here that changes identical with those I have described in the normal mucosa I was able to detect in the pathological stroma. In the immediate vicinity of the vessel lumen the protoplasm exhibits changes in every respect similar to those just described. Here the cell substance is broken up by the imbibed fluid which has accumulated in isolated spaces of greatly varying size. Here again, as in the last specimen, it is often seen that the spaces immediately abutting on the blood cavity are distinctly swollen inwards, proving beyond doubt, not only that the intravascular blood tension is not the factor responsible for the fluid escape by a mechanical filtration, but that, so far from this being so, the fluid has actually accumulated in the tissue under a pressure hydrostatically greater than that in the vessel lumen (Plates III. & IV.)

I may state that I have been able to recognise these changes in all my specimens of the normal premenstrual and the menstrual mucosa. They, I maintain, /

maintain, demonstrate beyond doubt that the orthodox conception entertained regarding the mode of the oedematous (and as I shall subsequently point out of the haemorrhagic) escape must be completely modified. I may state, also, that an examination of several hundred specimens of the mucosa (obtained fresh by curettage) has convinced me that the same tissue changes are responsible for many of the structural deviations of the stroma from the normal present under pathological circumstances. I have already referred to the changes in menorrhagia. I hope in a future publication to indicate the existence of similar factors in cases of metrorrhagia and leucorrhoea.

THE NATURE OF THE SO-CALLED TISSUE NETWORK OF
THE STROMA AND THE TRUE INTERPRETATION
OF THE INTERCELLULAR SPACES.

As was pointed out in the chapter devoted to the more general structure of the uterine stroma, varying ideas have been entertained by different writers regarding the exact structure of the finely drawn-out threads often seen in the mucosa and which frequently appear to be interlaced together to form an intricate network. By Leopold this was supposed to/

to be due to the presence of a fibrous connective tissue structurally independent of the cells. More recent research has proved the fallacy of Leopold's observations, and it has now been definitely shown that the protoplasmic processes are continuous with, and are composed of the same material as, the cell bodies.

It seems to me that the researches recorded in the preceding pages mark a still further advance in our knowledge of the intimate structure of the stroma. I have already pointed out that this must be considered to be composed throughout its entire extent of a homogeneous soft, easily displaced protoplasm. I have further adduced evidence in favour of the idea that the intercellular spaces are not, as is usually held, freely intercommunicating but consist, in the ordinary resting state, for the greater part each of a fluid cavity completely walled in on every side. The protoplasmic bridges between the cells are not, as they, at first sight, appear to be, cytoplasmic filaments but they are complete, though fine, films. (Page 53). It seems to me that the observations described in the last section lend additional support to this view, and they besides indicate that the many & varying appearances detected in the so-called "network"/

"network" correspond to the functional changes for which the stroma protoplasm is especially adapted. These appearances are not merely incidental but are of profound importance from the point of view of a proper understanding of the changes in menstruation, and as I shall subsequently show, in pregnancy.

Enough, I think, has been said in the preceding pages to prove that the network of previous writers in reality corresponds to the spaces in the protoplasm with their thinly drawn-out but complete envelope of cytoplasm enclosing the fluid which has been actively imbibed in response to the osmotic changes. The presence of this complete shell of cell substance was an absolute certainty in the case of the swollen intimal elements of the thickened vessels. In the same vessel it was present in the case of the fluid vacuoles in the inner aspect of the same vessel walls which were seen to project into the lumen. It is obviously present in the case of the vessel represented in Plates III & IV where the bulging fluid vacuoles are richly scattered along the inner aspect of the vessel wall. The manner in which the cell protoplasm of the stroma swells up with the imbibed fluid often to many times its original/

original size indicates beyond doubt that the water absorbed is contained within complete films of cytoplasm. (Figure 27.). These appearances thus prove beyond cavil that the so-called network formed by interlacing threads of cell protoplasm in reality corresponds to an agglomeration in the cytoplasm of fluid which has been actively imbibed and which is contained in spaces separated by complete walls. The attenuated portions of protoplasm are films and not filaments.

The fact that the protoplasmic changes during menstruation are found to be exhibited in an identical manner by all the different elements of the stroma (intima, media etc) is confirmatory evidence of the strongest kind in favour of the interpretation of the structure of the stroma which I have previously advanced. The lining and supporting cells were seen to be structurally similar to the stroma elements. They are now seen to be functionally identical.

The above observations lend added favour to the idea previously advanced that the intercellular spaces of the resting state correspond to fluid vacuoles, each completely shut in. In proof of this I pointed out that as a rule in section the spaces are/

are seen to be completely encircled by the fine protoplasmic bridges, and that where the opened out stroma cells take part in the formation of the wall of an expanded vessel the red corpuscles are often perfectly retained. The same phenomena is often seen where the red cells are being drawn into the stroma tissues; they are often seen to extend just so far as such a completely walled-in space. In figure 19 this is well shown. Four red corpuscles which have passed into the surrounding tissue from the opened-up vessel are seen to be lying right up against the fine wall of a space, where they have been retained, in all probability because of the intact protoplasmic film. The cavity of the space is devoid of the corpuscles.

These observations, it seems to me, force us to the conclusion that the structure of the stroma, consisting as it does of a homogeneous and easily displaceable protoplasmic surface, is especially devised for the free play of osmotic and diffusion forces.

While I am convinced that the description of the structure of the mucosa which I have given applies to every part of the mucosa, I am unable to make any definite statements regarding the presence or absence of any continuous lymph channels. All I do claim is that the orthodox conception of the intercellular spaces, in view of my observations, demands serious/

serious modification. Whether or not some few of these spaces differ from their neighbours in being united together to form a continuous lymph track I can neither assert nor deny. In the course of my investigations I have never seen any appearances to suggest the existence of such lymph vessels. It seems to me likely that, as the majority of the inter-cellular spaces are completely walled-in there will be in the resting state a perfect arrangement for a free osmotic diffusion of lymph throughout the stroma, the fluid streams carrying nutriment to, and effete products from, the isolated portions of the protoplasm. It seems to me, also not unlikely that in this way the lymph stream towards the muscular wall of the uterus will be determined. This conception, though somewhat conjectural, would seem to be in consonance with the more recent research into the mechanism of the capillary circulation and that by means of which the tissues are supplied with their nutriment. For example Leonard Hill states that "the influence on the capillary circulation of osmotic and surface energy can be no less than that effected by the heart and vaso-motor system, and is, probably, as important in controlling the flow of blood". We have seen/

seen that the stroma of the uterine mucosa is structurally to be looked upon as a spread-out osmotic machine.

EXPLANATION OF THE HAEMORRHAGE INTO THE STROMA DURING MENSTRUATION.

We have seen that the fluid constituent of the blood is sucked into the tissues in response to a universal increase in the osmotic tension of the stroma protoplasm. This change we have seen precedes the corpuscular escape. By it the stroma cells and the walls of the vessels are teased apart, in this manner preparing the way for the exit of the red cells.

I have shown how the escaping fluid is able with ease to displace the soft stroma protoplasm, in which it collects in vacuoles of varying sizes. The extraordinary facility with which this displacement occurs would seem to warrant the conclusion that the consistence of the protoplasm is somewhat of the order of a soft jelly.

In view of these facts it is not difficult to understand how the continual and, in all probability comparatively powerful stream of fluid passing/

passing from vessel to tissue should lead to a dragging out of the red cells. Of one thing, however, we may be certain that, whereas by the very nature of the osmotic stream the fluid diffuses freely across a protoplasmic sheet, for the leakage of the red cells a complete gap is essential. This fact has been repeatedly borne in upon me in the course of my investigations. I have pointed out, for instance, how the red cells are often held back, while the fluid is obviously freely leaking, by such a fine film as passes between two cells (Plate I. and figure 19.). These facts clearly explain how in the premenstrual phase there may be an extensive oedema with little or no haemorrhage.

I have pointed out how, by a disappearance of the cytoplasmic partitions, there may be an amalgamation of adjacent fluid spaces. This may be due to a mere mechanical giving way or it may be due to a fluid imbibition by the pellicle of protoplasm. By the fusion or expansion of the spaces large clear territories may result. This ready detachment of the sheets (again determined by the consistence of the protoplasm) will amply account for the corpuscular escape. Whether the cells can only pass along continuous tracks previously prepared for them by the fluid accumulation it is impossible to say with certainty/

certainty. It seems to me, however, more than likely that if the osmotic fluid stream from one side to the other of a protoplasmic film be appreciable, any red cell carried up against it will tend to pass across. This may cause an immediate and complete giving-way of the whole film or, what is not unlikely in view of the previous investigations, the gap may again close up by a flowing together of the protoplasm.

In any case it seems certain that the direct cause of the haemorrhagic escape is the osmotic stream of fluid created from vessel to tissue by the active stroma changes.

EXPLANATION OF THE FORMATION OF BLOOD

LACUNAE IN MENSTRUATING MUCOSA.

In view of these observations it is not difficult to understand the manner in which the comparatively large blood lakes or "distended capillaries", the exact structure of which I have described in detail (Plates I&II), are formed in the premenstrual and the menstrual mucosa. It would seem at first sight not improbable that they are formed as the result/

result of the constant and widespread imbibition of fluid in the superficial regions of the mucosa. This, it is clear, must determine an increased flow of blood along the vessels behind. That this explanation, however, does not account for the formation of these lacunae is proved by finding them in the most superficial regions of the stroma. We have already indicated that the mechanical influence of the intravascular pressure does not account for the passage of the fluid from the vessels that opens up the surrounding stroma. The same considerations that warranted this conclusion would seem to apply to the vascular expansion. As in the case of the active tissue imbibition the cause of the expansion at any point must be dependent on purely local changes. I have pointed out that the opening of the wall at any particular site in an enlarging vessel is due to a disappearance of the protoplasmic film separating the lumen from the immediately adjacent tissue space. How does this occur? It seems to me likely that it takes place in a manner represented in Plate III. Here the vessel is still small but it is obviously in the process of expansion. This is determined by a bulging and giving-way of the corresponding tissue film towards the lumen. This immediately carries the lumen/

lumen a degree further out. The same process by involving the entire circumference of the small vessel will result in a new and expanded wall, in which the stroma cells are included. So the change will go until a large sinus is produced. We thus see that the expansion is due to the same osmotic changes to which I have repeatedly called attention. In a subsequent section I shall demonstrate exactly the same process, only in a clearer manner, in the wall of the pregnant tube.

RÔLE OF THE EPITHELIUM IN DETERMINING THE CHANGES PRESENT.

As has been repeatedly pointed out by other observers the oedema and haemorrhage during menstruation is often localised in a remarkable manner to the neighbourhood of the surface epithelium or glands (Figure 13.). Under the lining epithelium the extravasated blood often collects either in the form of a continuous sheet or of little haematomata.

The explanation of these phenomena is not difficult to find when it is remembered that during the menstrual process there is a continual fluid and blood/

blood escape from the epithelial surface, and this especially in regard to the lining cells. The opening up of the adjacent regions of the stroma is probably to be looked upon as the result of the tendency of the fluid to escape into the regions of least resistance - it passes more readily towards the regions from which it is escaping.

As has been seen by a study of the literature there is some uncertainty regarding the exact manner in which the red cells make their escape into the uterine cavity. The fluid is probably passed on by a secretory activity. The more recent researches would tend to indicate that there is little, if any, epithelial shedding during menstruation. This leaves only two methods of accounting for the leakage of the red cells. It must be through or between the cells. In some of my specimens I have detected the presence of clear tracks between the cells, in some cases large enough to accommodate the red corpuscles, but as I have stated on a previous page I have never noted the red cells actually passing through in quantity. Is it possible that these appearances indicate the tracks by which the cells escape, and that in the process of hardening of the specimens, the shrinkage has tended to force out the cells?

S U M M A R Y.

1. The oedematous infiltration of the tissues, which precedes the haemorrhagic escape, is due neither to a mechanical displacement or filtration of fluid from the vessels nor to a secretory activity of the intimal cells.
2. It is dependent on protoplasmic changes which result in an active imbibition of fluid from the vessels, by a process of osmosis. So far as we at present know this change is due to a widespread liberation of crystalloidal elements in the tissues. The fluid diffuses from the vessels, teasing out the vessel walls and the surrounding stroma in the process.
3. The stroma & vessels are especially adapted for such a process by virtue of the structural peculiarities previously noted. Additional evidence has been advanced in support of the belief that the intercellular spaces are completely walled-in under ordinary circumstances. The so-called network corresponds to the fine films separating the fluid/

fluid chambers of the functioning stroma protoplasm. The stroma is a potential blood sponge.

4. The opening-out of the stroma and vessels prepares the way for the escape of the corpuscles. This occurs by a process of diapedesis, and also as the result of a wholesale displacement of the vessel wall and stroma. Into the composition of the wall of the sinuses or lacunae stroma cells largely enter.
5. These vascular changes are probably chiefly due to the active osmotic streams radiating from the vessels into the tissues. How far the ordinary vis a tergo dependent on the heart force acts it is impossible to say. It seems likely that it is insignificant.
6. The exact process by which the blood cells escape into the uterine cavity these researches do not elucidate. Is it mechanical or of a nature similar to that above described?
7. The tissue changes are, so far as we at present know, due to some material (secretion or enzyme?) liberated by the ovary.
(In/

(In subsequent sections I shall endeavour to prove that the bio-chemical substance derived from the chorionic cells produces changes in the maternal tissues in many respects identical with those described in the menstruating mucosa.)

SECTION III.

MODE OF ACTION OF CHORIONIC STRUCTURES ON MATERNAL TISSUES.

PREGNANT TISSUE.

INVESTIGATION OF THE ACTION OF THE CHORIONIC
STRUCTURES ON THE MATERIAL TISSUES OF THE
EMBRYO. I propose to discuss the material changes
induced by the chorionic structures in the
following regions:-

SECTION III.

MODE OF ACTION OF CHORIONIC STRUCTURES ON MATERIAL TISSUES.

PREGNANT TUBE.

THE INFLUENCE OF THE CHORIONIC CELLS ON THE MATERIAL
TISSUES, AS STUDIED IN THE PREGNANT TUBE

The material used for this investigation
consisted of nine specimens of human pregnancy. They
were all removed by operation and they were, there-
fore, obtained in a perfectly fresh state. In the
specimens

INVESTIGATIONS carried out for the PURPOSE of DISCOVERING the NATURE of the ACTION of the CHORIONIC CELLS on the MATERNAL TISSUES, especially with REGARD to the CHANGES in the BLOOD-VESSELS.

I propose to discuss the maternal changes induced by the foetal elements as detected in the following regions:--

- (1) The wall of the Pregnant Tube..
- (2) The uterine wall in those cases where foetal fragments of the placenta are retained.
- (3) The uterine and other tissues in chorion-epithelioma.
- (4) The uterine tissues in normal pregnancy, and the function of the decidual membrane.

The INFLUENCE of the CHORIONIC CELLS on the MATERNAL TISSUES, as studied in the PREGNANT TUBE

The material used for this investigation consists of nine specimens of tubal pregnancy. They were all removed by operation and they were, therefore, obtained in a perfectly fresh state. In the shortest/

shortest possible time they were, in each case, placed in Pick's solution (No I) for hardening. The desired portions of the tubal wall were removed and mounted in paraffin. They were then cut into serial sections, varying in number from 40 to 2,000. Out of the total number of specimens examined, I propose to limit my description of the histological details to five of them, in which, with one exception, the fact that the embryonic structures are in a perfect state of preservation indicates that the changes present in the tube are not dependent on the process of degeneration or repair subsequent to the death of the chorionic cells. The reason for making the exception mentioned will become evident in a later part of the research. The approximate durations of the pregnancies are 7-10 days (?), 2-3 weeks, 2 months, $3\frac{1}{2}$ months, and 4 months.

In the wall of the pregnant tube it is found that where the chorionic cells come into contact with the maternal structures there is present a zone of markedly degenerated tissue - the cell outlines are obscured or have disappeared, the nuclei have disintegrated and there is produced a homogeneous necrotic surface which forms the confines of the ovum bed. One of the most characteristic features/

features of this necrotic zone is the extensive infiltration of the tissues with red blood corpuscles. (Plate VIII). There is usually present also a marked oedematous exudate.

Imbedded in this degenerated tissue, which is formed chiefly of disintegrated muscle, there are often seen cells which contain a pale nucleus and often attain a very large size. The main distinguishing feature of these cells is the enormous increase in the cell-body, a trait which identifies them with the decidual cells in the uterine mucosa, which are found in normal and also in tubal pregnancy, and which are produced by an enlargement of the stroma connective-tissue elements. It seems certain that in the tube, also, these cells are connective tissue in origin. A mass of degenerating tissue containing such cells is shown in Plates VII. and VIII.: it immediately borders on the intervillous space. The structure of the tubal wall, in which the connective tissue elements are never found massed together as in the uterine mucosa, precludes the possibility of a decidual formation occurring to the extent present in the uterus. In the tube the change is, for the most part, indicated only by the presence/

presence of these transformed cells scattered irregularly about the muscular tissues. An exception, however, must be made to this general statement in view of the fact that the connective tissue of the mucous ridges of the tube, which corresponds closely to the stroma of the uterine mucosa, is able to undergo a change identical, in many respects, to that found in the decidual membrane of ordinary pregnancy. The importance of this fact I shall refer to in greater detail in the course of this research.

Whilst the above-mentioned vascular and tissue changes are detected in the most marked degree in the immediate vicinity of the ovum, they are by no means limited to this region. By most observers they are recognised as due to some bio-chemical influence, probably an enzyme or enzymes, liberated by the cells of the developing chorion. The probable nature and properties of this foetal influence I shall discuss in greater fulness in a subsequent section; in the meantime I shall follow the usual practice and refer to it under the rather vague terms of "chorionic influence", "foetal activity", etc.

As the study of the pregnant tube has been approached in order, if possible, by a process of analogy to cast some light on the way in which the uterine/

uterine mucosa reacts in the case of a normal pregnancy, and especially on the alterations exhibited by the maternal vessels in the provision of an ample supply of blood for the engrafted ovum, it will be necessary to trace the vascular changes in the tubal wall in some detail. It will be helpful if I preface my description of these changes as detected in my specimens by a short resumé of the more recent literature on the subject.

As far as I can discover from a study of the literature on tubal pregnancy, the expression of opinion is unanimous in favour of the belief that the developing chorionic cells procure their requisite blood supply by destroying the maternal vessels which they encounter in their advance. As to the exact nature of the destructive activity with which the chorionic epithelium is endowed, there is some divergence of opinion, and not a little ambiguity in the literature. Some authors, such as Heinsius,⁽¹⁾
⁽²⁾ ⁽³⁾ ⁽⁴⁾ ⁽⁵⁾
 Fellner, Raschkes, Schambacher, Berkeley and Bonney,
⁽⁶⁾
 Whitridge Williams and others would seem to incline to the view that the opening up of the vessels is due to an active cellular invasion of the maternal tissues by the chorionic off-shoots - these after becoming engrafted on to the tubal wall, destroy and/

and replace the maternal structures, and, in this way, create gaps in the vessel walls. Other observers such as Kroemer⁽⁷⁾ and others endeavour to explain the phenomena not by actual cellular incursions of this nature but rather by a sort of softening and corrosion of the tissues. When the process involves the wall of the vessel this gives way, permitting an escape of blood round the advancing foetal structures. Still other writers, for the purpose, it would almost seem of avoiding committing themselves one way or the other, either hazard no statement at all, or employ such indefinite phrases as "the influence of the chorionic cells", "the bio-chemical activity of the foetal cells".

For the purpose of testing the validity of these views, and, if possible, of arriving at some definite conclusion on the subject, I have carried out an extended investigation in my specimens. To obviate as far as possible the risk of an erroneous interpretation of the appearances presented, the examination has been conducted exclusively by means of serial sections.

As regards the first of the above-mentioned views, namely that the opening of the vessels is dependent/

dependent on a projection of the chorionic buds into the maternal structures which become destroyed and replaced, the evidence derived from my specimens is, at first sight, somewhat ambiguous. The specimens exhibit the well-known appearance in the fact that, round the periphery of the ovum bed, the foetal cells have, here and there, become engrafted on to the wall of the tube. Where this has occurred, the portion of the tube wall appears to be eaten away and replaced by chorionic cells, which are incorporated with the maternal tissues or are unattached, and lie free in bays, formed in the surface of the tubal wall, forming the confines of the ovum bed. Where the foetal ectoderm has encountered a vessel in its progress the same process has taken place, till in some cases the embryonic cells are seen to have bored right through the vessel and project into the lumen. This action is certainly usually not difficult to discover, though in my specimens it is not present to any considerable extent. The true interpretation of this appearance, I shall describe in a later section. In the meantime, I would suggest as a logical conclusion that per se an invasion of the wall of a vessel by the chorionic/

chorionic cells would not be likely to lead to a wholesale gaping without some other process e.g. softening. It seems likely that the replacement of the destroyed tissue by the foetal cells would plug the breach produced, and would thus prevent the mechanical escape of the blood.

Whilst the process just described culminates in the part of the villus which is free in the vessel lumen becoming bathed in blood, it does not account for the wholesale gaping of the maternal vessels round the wall of the foetal cavity, which pour their blood into the intervillous reservoir. In some regions, it must be admitted, it is possible to detect the spread of the chorionic cells for some distance along the inner aspect of the wall of a vessel, which has become opened out into the intervillous space. In my specimens this was detected in only a few places and is amply accounted for by the fact that it happened to be the spot at which the chorionic cells had alighted. That the free ends of the villi floating in the intervillous space may be carried into the open mouths of the vessels has been repeatedly described by previous observers. After gaining an entrance the villus may/

may grow for a considerable distance along the vessel. This process, which has been termed by (3) Veit "deportation of the villi" occurs both in tubal and in uterine pregnancy (Figure 56). Detachment and carrying away of foetal cells from these intravascular villi has been advanced by the same author to explain the etiology of eclampsia. The entrance of these villi into the vessels might at first sight suggest that the apertures produced in the vessel wall had been due to a direct spread of the foetal villi through the wall, and that their further growth had given rise to the appearances noted above. This argument, however, is undermined by the demonstration of Veit, that the villous growth has occurred only along the veins, and he, therefore, suggests that their situation within the vessel lumen is to be explained by the fact that they were carried there by the force of the blood stream subsequent to the opening up of the veins.

That a direct cellular invasion of the foetal villi is discredited, as a satisfactory explanation of the phenomena is proved, in addition, by the fact that in many places the mouths of the vessels which discharge their blood into/

into the embryonic space are found to be situated at a distance, sometimes considerable, from the sites where the foetal cells are engrafted on the tube wall (Plate VII). As a matter of fact, in my specimens, this engrafting has occurred only to a comparatively small extent and certainly in a degree much smaller in proportion than the number of the opened-up vessels. The only logical conclusion from these observations is that the vascular gaping is produced by some influence other than the process conjectured by the aforesaid authors. It would seem to be in the light of these facts that some authors have endeavoured rather to attribute the destruction of the vessel walls to the softening or corroding action of some material liberated by the chorionic cells, and this explanation would certainly meet the case much more satisfactorily. It would seem not improbable that in advance of the developing villi, the structures of the tube wall are by this means softened and dissolved, and the vessel walls sharing in the process, that the blood circulating in their channels is liberated and discharged, through the gaps thus created, into the intervillous space. This view affords an ample explanation of the above-mentioned facts, that the vessels opened up are often situated in/

in regions at a distance from the infiltration of the chorionic cells. This interpretation of the phenomena, also, possesses the advantage of explaining the fact, which, though remarkable has received only a scanty attention in the literature, namely that the dimensions of the ovum cavity in the tube as in the uterus are greatly in excess of the requirements of the ovum and its villous projections. This provision, of course, is necessary for the existence of a blood filled intervillous space, and is in all probability attained in part by a dissolving influence such as we have described. In a subsequent section of this research an attempt will be made to demonstrate that different factors, however, are at work in the case of pregnancy in the uterine mucosa.

We thus see that whilst the facts are completely at variance with the views entertained by the first class of observers mentioned in a previous paragraph, they conform at first sight with the opinions advanced by the second class. Do these, however, constitute a full and efficient explanation of all the phenomena? My researches have led me to answer this question in the negative. My specimens have furnished evidence which, in many respects, is fundamentally/

fundamentally opposed to this simple explanation.

If we examine the tube wall behind that part forming the limiting surface of the ovum cavity, we find that the vessels exhibit remarkable changes, changes which must be considered as casting important light on the manner in which the vessel lumina in immediate proximity to the ovum are brought into direct continuity with the intervillous space. These changes are most evident in the region of the tube forming the wall of the gestation cavity and become less and less marked as this is left. They are, however, still detectable at a considerable distance from the site of the ovum.

In Plate VII is shown the condition typically present. In the lower part is seen the region of the intervillous space. At this region no villi are present. On the right side, opening into this by a wide mouth, is seen a distended vessel. There are no chorionic cells in its neighbourhood, which might have accounted for the removal of its wall by a direct infiltrative and destructive influence; this fact was confirmed by tracing the sections in series throughout the entire extent of the gaping vessel orifice. In the neighbourhood of this vessel/

vessel several epithelium-lined spaces are seen; these correspond to a diverticulum from the tube lumen which had extended for a considerable distance into the muscular portion of the tube wall, and which has been cut across in three different regions of its course. To the left of the gaping vessel is seen another blood filled space, separated from the intervillous blood region only by a thin lamina of the degenerated tube wall, which at one part is extremely attenuated and is, as a matter of fact, on the point of giving way. This space corresponds to a distended blood vessel. Another vessel somewhat smaller than this, is shown still further to the left of the plate. The lesson which this plate is more especially intended to convey is to be seen in the fact that the blood corpuscles are straying in quantity from the vessel lumina into the surrounding region of the tube wall, and, at the part where there is left only a thin partition between the two blood spaces, the corpuscles are actually seen to be passing in considerable numbers through this ne-
crossed region of the tube wall into the intervillous space. In the immediate proximity of this vessel there were present no chorionic cells. The great distension /

distension exhibited by the vessel and the exodus of the red corpuscles into the intervillous space even before there was an actual breach in the continuity of the vascular wall would tend to suggest that there must be some influence at work conspiring to soften and tease apart the vessel boundaries, an action which leads, in the case of those vessels in immediate proximity to the gradually receding surface of the ovum cavity, to an increasing thinning out of the wall, which ultimately gives way, permitting the affected vessel to contribute its share to the intervillous reservoir. It can easily be seen that, in a short time more, the vessel exhibited in Plate VII. would have been brought into free communication with the large blood space.

If we can arrive at some definite conclusion as to how this process occurs, we shall be furnished with important information regarding the mode of action of the chorionic ectoderm in the tubal wall and, by analogy, we may glean some evidence of importance in a similar enquiry with respect to the manner in which the uterine mucosa reacts to the growing ovum in the case of an ordinary pregnancy. In the first place, in the case just cited, which represents the typical condition in these parts of my specimens in which we can follow the process/

process in all the stages short of an actual whole-sale breach in the vessel walls, it will be freely admitted that the opening up of the vessel cannot be dependent on a direct invasion by the chorionic cells. It is obvious, in addition, that it is not due to a softening and destruction of the tube wall, which advances gradually from the bounding surface of the gestation sac outwards, opening up the vessels encountered en route. It may, at first sight, seem possible to explain it as due to a gradual expansion of, and blood escape from, a vessel due to the soft and distensible nature of the medium in which it courses, and to an ultimate giving way when the tissue between the two bloods is reduced in thickness to such an extent as to be unable to resist the intra-vascular blood pressure. This simple interpretation, however, does not solve the problem and in proof of this I submit the following facts.

As already mentioned the portion of the tube wall bordering on the ovum cavity is extensively infiltrated with red blood corpuscles. These are especially numerous round the vessels, many of which are greatly distended. This condition is, however, present, sometimes to a marked degree, even at a considerable distance from the ovum. In Plate/

Plate VIII is shown a section demonstrating these appearances in a lucid manner. In the lower part is seen the intervillous space, in which several villi are pictured. The immediately adjacent tube wall is undergoing a marked fibrinous degeneration, and is interspersed with extravasated blood. Above this a less necrosed portion of the tubal wall is shown. Here and there, especially round the blood vessels, which are somewhat distended, there is likewise a haemorrhagic extravasation. In figures 57 58 and 59 are shown such vessels. The method of the blood escape is well shown; the red cells are seen streaming out through the wall into the surrounding tissue, which has been opened out by a previous oedematous exudate. With the red cells there are also present considerable numbers of leucocytes of all types, the polymorphonuclear predominating. The tissues in which the changes are taking place are softened and degenerating.

With regard to the distension of the vessels there is a point of considerable interest and importance. This has already been demonstrated on Plate VII, and it is again well seen in the figures here reproduced. The increase in the diameter of the vessel lumina often does not occur in a/
a/

a regular and uniform manner such as we associate in other parts of the body with an enlargement due merely to an increased intra-vascular tension. The distension in this case is of an uneven, sometimes very irregular nature. The walls open out more at one part than another, the result being the transformation of the ordinary rounded contour into one ragged and uneven. In a short time the confining wall becomes completely teased asunder and the blood comes to be contained in an uneven space formed entirely by the opened out surrounding tissues.

^{&58}
 In figures 57 are shown two sections across the same vessel at different parts of its course. In the first place the vessel is seen to have still retained its even contour, the wall being preserved. In the second figure, on the other hand, this appearance has been replaced by an extremely uneven vessel boundary. These figures indicate clearly the manner in which the vessel expansion occurs. It takes place at the expense not only of a displacement of the boundary wall but also of a displacement of the adjacent tissues, a change which steadily progresses till the originally comparatively small vessel is transformed into a large and still increasing/

increasing blood space or cavity. Even then round the margins of this there is often seen on sections to be a free exodus of the contained corpuscles into the adjacent tissues. This condition is present round the entire circumference of the ovum cavity often becoming as already noted more and more evident as the boundaries of the intervillous space are reached.

In the proximity of the ovum the histological changes in the tissues are obscured because of the degree to which they have succumbed to the fibrinous degeneration, and, to obtain information of an accurate nature regarding the actual changes present, we have to carry our attention to the vascular alterations in the tube wall at a greater distance from the ovum. The evidence thus acquired will enable us more readily to understand the changes to which I have referred. As we pass further and further from the gestation cavity we find a gradual diminution in the grossness of the vascular changes. The crumbling away of the walls with a wholesale extravasation of the contained blood into the surrounding tissues, which we encounter in the immediate proximity of the developing/

developing ovum, becomes gradually less and less evident and is replaced by a softening and expansion of the vessels with here and there small areas of blood escape into the vessel wall and the adjoining tubal tissues. Throughout the entire extent of the affected tube there are found large irregularly shaped, sinus-like blood spaces, resembling, in every respect, the blood sinuses which develop in the muscular wall of the uterus during ordinary pregnancy. The mode of formation of these blood tracks in the tubal wall and its possible bearing on the manner of origin of the similar uterine lacunae will be fully described in a subsequent section of this research.

In endeavouring to determine the manner in which the teasing out and gaping of the vascular wall occurs during tubal pregnancy our purpose will be best accomplished by directing our attention, in the first place, to the changes exhibited by the small thick walled vessels at a considerable distance from the ovum, in regions where the condition is definitely established. Passing thence by degrees to the region of the gestation cavity we are enabled to trace the process from a mere softening to/
The adjoining tissues of the tubal wall

to the wholesale destruction of the vessel walls in the immediate vicinity of the embryo.

In figure 60 is shown a section of a small vessel, the wall of which is represented by a homogeneous fibrinous material, in which there are present a number of well-preserved nuclei. Pervading the wall a number of clear spaces are seen, which on section are represented by vacuoles. These, though present throughout the entire thickness of the wall, are most evident immediately under the endothelial layer. The changes, which are present here, and which, as will be subsequently shown, are found widely scattered throughout the tubes, might at first suggest the existence of a fatty degeneration of the tissues, the clear spaces corresponding to fat globules, which have been dissolved in the preparation of the section. That this is not so is easily proved by preparing the fresh specimen, and then staining it, for fat. I mention this point here to dispose of it once and for all. The resemblance to a fatty degeneration, which appears at first sight, will be found to completely vanish with a fuller study of the changes.

The adjoining tissues of the tubal wall are/

are spread apart by an oedematous exudate. The oedematous infiltration of the vessel wall and surrounding structure represents a condition, which, as we have already mentioned, is existent in every part of the pregnant tube. It is usually most evident, as shown in the accompanying figure, in the immediate environment of the vessel, and it is due to some influence leading to an increased escape of fluid from vessel lumen to tissue spaces. The well supported vascular walls are for the most part not involved in the process to the same degree as the more displaceable structures of the tube, but that they share sooner or later in the change is shown by the figure.

The structural changes underlying this dropsical infiltration of the vessels, which play an important rôle in the softening and ultimate giving way of their walls are, in all probability, closely allied to those which operate in the production of oedema in general. Occurring, as it does, in the condition which we are investigating, in the wall of a markedly degenerating tube, it is possible that factors may be introduced which differ in kind or degree from those concerned in the production of oedema/

oedema in other regions. The factors which must concern us in an investigation into the causation of the dropsical condition just referred to, are any or all of those responsible for an increased transference of fluid from vessel to tissue, and are obviously identical to those which operate in the production of oedema elsewhere. These factors are (1) the blood in the vessels. (2) the endothelial lining of the vessel and (3) the structures external to this, namely the rest of the vessel wall, in the case of vessels larger than capillaries, and the neighbouring tissues of the tube.

The numerous attempts which have been made in recent years to cast light on the difficult problem of the production of oedema have, for the most part, been based on the supposition that the mechanism at work in the pathological escape of fluid from the vessels, which constitutes this condition, is, to a large extent, similar to that concerned in the physiological transmission of the lymph fluid. The investigations into the manner in which lymph is formed under ordinary conditions have been largely approached by the study of the variations in the lymph flow under differing artificially/

artificially produced circumstances, the results thus gained being employed in an attempt to detect the factors normally in operation. These investigations have been conducted, for the most part, by experimental methods of research. The different conceptions entertained may, for convenience, be grouped under two headings, according to the factors supposed to dominate the process.

- (1) The first or the so-called "Physical Theory" attributes the phenomena of lymph escape to purely physical laws. The simplest conception⁽⁹⁾ was that associated with the name of Ludwig, who supposed that the process was due to a mechanical filtration of fluid through the capillary wall from the vessel lumen, where the pressure is higher, to tissue, where it is lower. This, in the hands of later investigators, has been added to, so that now-a-days the forces of diffusion and osmosis, depending on a chemical inequality of the fluids on either side of the capillary membrane, are held to play a prominent part. To completely account⁽¹⁰⁾ for all the phenomena, Starling has added still another factor, namely a variation in the permeability of the capillary walls in different regions./

regions. All the investigators, who incline to this physical interpretation of the phenomena, agree in believing that variations in the intra-vascular pressure of the blood must play an important rôle in the process, but there is still a considerable divergence of opinion as to the extent to which alterations in the tissues themselves determine the fluid exchange. The experiments of Lazarus-Barlow, Asher, Bainbridge and others, would tend to prove beyond doubt that the quantity of the lymph formed is controlled to a large extent by the activity of the tissue elements.

According to Starling, Asher and others the metabolic changes induced in the tissues during their activity result in a breaking down of the complex protein, carbo-hydrate and fat molecules to simpler ones. In the process there is a liberation of crystalloids which, passing into solution, increase the osmotic tension of the tissues and determine a passage of fluid from the vessels. This conception of the process is certainly consonant with recent research on the chemico-physics/

(14)

physics of the cell. (vide Moore).

- (2) In the second category there is the so-called "Vital Theory", associated especially with the name of Heidenhain.⁽¹⁵⁾ This investigator and his supporters have carried out a large number of experiments with the object of demonstrating that the physical laws of filtration, diffusion and osmosis do not suffice to explain all the phenomena, and they have adduced as a necessary element a secretory activity on the part of the endothelial cells. The many variations, normal and experimental, which are exhibited in the amount of the lymph flow, are by them to be attributed to variations in the vital and selective activity of these cells.

Workers on the mode of production of a pathological accumulation of fluid in the tissues or oedema have, in their investigations, pursued closely the lines indicated by those engaged in the quest after the secret of physiological lymph formation. It is obvious that a scrutiny of the factors concerned in the transmission of fluid from vessel to tissue, with in addition, any conditions which retard or obstruct the escape of the fluid/

fluid thus formed, must embrace all the agents responsible for the occurrence of oedema. It is obvious that any disturbance of the different conditions, normally acting in harmony, may determine the production of a dropsical state. This disturbance may be of the nature of an increase in the blood pressure or a change in the composition of the blood, it may depend on a pathological state of the endothelium, or an abnormal composition of the tissue elements, resulting in the production of diffusion or osmotic currents.

As already indicated a study of my specimens has convinced me that the changes operating in the softening and opening up of the vessels in the tubal wall during pregnancy in that region are intimately bound up with the structural alterations which lead to an oedematous infiltration of the vessel walls and tubal tissues. This is associated with a teasing asunder of the elements which constitute the walls of the vessels and is followed sooner or later by a breach in continuity with the production of a track or tracks leading directly from vessel lumen to tissue or intervillous space. It is obvious, therefore, that any investigations which cast/

cast light on the mode of production of this dropsical escape must carry us a long way towards a proper understanding of the manner in which the ovum engrafted in the tube wall is furnished with its blood supply.

In conducting this enquiry I have followed the lines indicated by previous workers on the production of oedema in so far as this includes a scrutiny in succession of the possible determining agents. My investigations, however, have necessarily differed from theirs in the fact that I have carried out my research by the aid of the microscope and not by means of experimental measures. So far as I know the observations here recorded incorporate the first attempt ever made to elucidate the difficult problem of oedema-production by means of an actual systematic and histological survey of the tissue elements concerned in the process. This fact would indicate that any light cast on the subject by this means will, in addition to affording us assistance in our local enquiry, add evidence of a different nature from that hitherto obtained in regard to the study of oedema in its more general aspects.

In approaching the study of the changes responsible for the oedematous ploughing up of the vessel/

vessel walls and tube tissues to which we have already referred, it will be well to consider them under the various headings already indicated, namely (1) alterations in the blood (2) changes in the fine membrane formed by the endothelial layer and (3) changes in the rest of the vessel wall and the surrounding tissues. In our enquiry, vessels thicker than the capillaries have been chosen for a reason which will soon become evident.

ALTERATIONS IN THE BLOOD.

As regards the blood contained in the vessels, changes may occur in two different directions, in the form of altered composition or altered pressure. An alteration in the constituent elements of the blood cannot *per se* lead to an increased escape of fluid through the vessel walls. Any interchange of fluid between blood and tissue, in the form of an increased transference from vessel, must be dependent on an alteration in endothelium or tissue, except in the case of a mechanical filtration, which comes into consideration under the heading of altered pressure. In this place, however, it is necessary to state that the bio-chemical material/

material emanating from the chorionic cells, probably of the nature of an enzyme, and which we have seen must be the primary causal agent in the changes under discussion, may possibly be carried to the affected regions by means of the blood stream. This reservation which does in no way affect our present argument, will be more carefully discussed in a subsequent part of this research.

Is the dropsical exudation, then, to be explained by a mechanical escape of fluid from vessel lumen into vessel wall and thence to the tissues? This explanation would, at first sight, seem to accord with the established facts, namely that in the first place, during pregnancy there is a well-marked local congestion and probably increase of intra-vascular pressure, and that, in the second place, there is a degenerative softening of the tissues. These two conditions acting in consort might be supposed to explain the facts adequately, the first resulting in an increased transudation of fluid across the vessel walls, the second allowing of an easy detachment and displacement of the elements of the vessel wall and tissues. That the phenomena, however, are not amenable to such an easy interpretation/

interpretation is proved by a study of the histological changes present.

The ploughing up of the vessel walls by the watery escape may, for purposes of description, be divided into three stages marked off from one another more or less roughly. In the earliest stage the condition has involved the inner portion of the wall, which is seen to be beset with a number of fluid tracks, which on section appear as clear vacuoles. In the next stage the condition has involved the entire thickness of the vessel wall, whilst, in the last stage, there is a wholesale ploughing-up of the wall with the creation of gaps which establish a direct communication between vessel lumen and tissue spaces. Throughout the process the surrounding tissues of the tubal wall become the seat of a watery infiltration, whose intensity in many places is seen to vary in proportion to the degree of damage of the vessel wall. In some cases it is easy to detect varying degrees of these changes in different parts of the same vessel. In Figs. 60, 61, & 62 are shown examples of the first stage, in Figure 63 one of the second stage, these being from different sections of the same vessel, whilst in Figure 58 is shown an example of the third stage. Here, besides a wholesale escape of fluid, which is readily recognised in the other cases, there has occurred an extensive haemorrhage into the neighbouring/

neighbouring tissues.

That a mechanical filtration into, and displacement of, softened tissues, does not suffice as an explanation of the phenomena is revealed by a more careful study of the changes. In figures 61, 66, 68 & 69, it is seen that the fluid, which has passed into the vessel wall and has accumulated in spaces toward its inner aspect, has led to a lifting up or projection of the endothelial cells into the vessel lumen in the form of distinct bulgings.

This is even better demonstrated in Plate IX. . In some cases this condition is associated with knob-like swellings formed of the individual cells, in other cases it is represented by a separation and bulging towards the lumen of the endothelial layer of cells, which have become detached as a sheet (Figure 65). These appearances, which I have been able to detect with ease in all my specimens of tubal pregnancy, demonstrate that, in the transference of the fluid from the vessel lumen which has accumulated in the inner part of the wall and led to a displacement of the endothelium, there has been in operation a force other than a mere mechanical filtration across a membrane from a region of higher/

higher to one of lower fluid pressure. In fact it is obvious that, so far from this being the explanation of the phenomena, the fluid leading to the endothelial uplifting must actually be under a hydrostatic pressure higher than that in the vessel lumen.

The extent to which this change occurs in different vessels and in different specimens varies within wide limits. As a general rule it may be laid down that the better supported the vessel wall, and the greater the success with which it resists the softening and exudative process, the more marked the involvement of the inner part of the vessel wall.

This fact is not difficult to explain. The greater the implication of the outermost parts of the vessel wall in the process, the more readily can the fluid, which is being abstracted from the vessel, be passed on, relieving in this way the fluid tension on the endothelial aspect. The force of these facts is emphasised by a study of figure 65. Here the fluid accumulation has occurred to such an excessive degree as to lead to a forcible detachment and inward projection of the endothelial sheet. It will be noted that in this vessel the outer part of the vessel wall has remained practically immune to the changes. These appearances, which are present in my fresh sections, demonstrate, moreover, that the force/

force determining the fluid exchange must be considerably in excess of that of the pressure of the blood in the vessels. In passing, it may be mentioned that the location of the structural changes to the innermost part of the vessel wall is, for the most part, most evident in those vessels, which exhibit a decidual reaction in their wall. The importance of these facts with regard to the function of the decidual cells will be more particularly referred to in a later section of this research.

A more careful examination of the exact histological changes associated with this dropsical condition of the innermost part of the vessel walls reveals some facts of considerable interest and importance. In some cases the oedematous exudate has collected under the endothelial cells. This is invariably the condition present when the fluid accumulation has occurred to any marked extent. When there is a wholesale detachment of the endothelial layer, such as is present in figure 65, it is obvious that the fluid must be contained for the most part, in a space entirely sub-endothelial in position. In other cases, however, the watery escape is associated with a fluid accumulation in the/

the endothelial cells. This hydropic distension of the individual cells, which in pathological textbooks is somewhat erroneously termed "vacuolation", is accompanied with a marked swelling of the cell, the cell substance being displaced by the accumulating fluid to the periphery where it is represented often merely by a fine film. The detection of this film of cell protoplasm is sufficient to indicate that the fluid accumulation has occurred within and not outside the cell. The distending fluid has likewise led to a displacement of the nucleus to the surface of the cell, and the result produced by the clear space, surrounded by the pellicle of cell substance, with the nucleus at the pole, has been designated by the term of the "signet ring" appearance. The changes in the nucleus are usually characteristic; it becomes flattened and drawn out, often occupying a large area of the circumference of the cell, and it is interesting to note that in the larger number of instances it is displaced towards the part of the cell projecting into the cell lumen. These appearances are well demonstrated in figures 60, 61 and 63. Another structural change of great interest is to be seen in the fact that the nuclear substance/

substance often appears to be drawn out in the form of strands which encircle the cell, sometimes passing round for a considerable distance. These appearances I have already referred to in the menstruating mucous membrane of the uterus.

In that region they were seen, as here, to be associated with an escape of fluid from the vessel lumen into the tissue spaces.

This hydropic distension of the cells is sooner or later followed by an escape of the contained fluid into the region immediately underlying. This would seem to be preceded in most cases by a disappearance or rupture of the intervening sheet of cell substance. It would seem not unlikely that, after the distension has occurred to a certain extent, the intra-cellular tension created will suffice to lead to a giving-way of the fine film, with an escape of the fluid. In some cases it is possible to recognise what appear to be the severed edges of this sheet. In figure 68 is shown a vessel in which there has been an escape of fluid from the region of the endothelial cell into the inner part of the wall. How far the distension of the cell can take place without a separation of the cell boundary it is difficult to say. In some specimens this/

this would, at first sight, appear to be very great indeed (Plate IX.). In these cases, however, it is more likely that what apparently looks like the boundary of a largely distended cell is, in reality, formed of the rounded wall of a space formed in the surrounding tissue. It is often seen that the fine partitions intervening between the contiguous, distended endothelial cells disappear, and in this way a track filled with fluid of varying lengths may be formed.

For the most part it may be stated that this alteration in the endothelial lining of the vessels is the more evident the better supported and therefore, the more immune to the fluid escape, is the condition of the outer part of the vessel wall. Conversely, with the teasing out of the adjacent part of the vessel wall there is apt to be an obscuring of the true nature of the process at work. Where the intra-or extra-cellular fluid accumulation has involved the innermost part of the vessel wall it may be taken as an indication of a process associated with an oedematous escape of fluid from the vessels. This point will be more particularly discussed in a subsequent section on the significance of endothelial vacuolation in oedema/

oedema formation.

In the second stage of the arbitrary division, which we made for the purpose of facilitating the description of the process, the condition which we have seen present in the innermost region of the vessel wall, has spread to the extent of involving its entire thickness. Here the oedematous infiltration of the vessel is represented by the presence of a large number of fluid tracks, which on section, often again look like vacuoles occupied by clear fluid. These spaces can often be recognised to be in direct continuity with those under the endothelial layer, and they can likewise often be traced directly into the peri-vascular tissues of the tube wall. In figures 63 & 97 are represented vessel walls exhibiting this later stage. In figure 63 in which such a fluid track has been exposed throughout its entire length in the section, the wall is seen to be channelled from the region of the sub-endothelial space right into the surrounding part of the tube wall, the tissues of which are ploughed up by a watery exudate. In all the specimens belonging to this stage there is still, however, no complete breach in continuity in the course of the/

the vessel wall, and whilst the change is associated with an increased fluid escape into the neighbouring tissues the teasing apart of the wall has as yet not taken place to the extent of permitting an escape of the corpuscular elements of the blood. The extent to which this oedematous softening of the vessel wall can occur, short of the occurrence of a complete breach, varies within wide limits in different vessels of the same thickness. In some cases it is indicated by a number of small vacuolated spaces scattered irregularly throughout the wall. This condition is seen in figures 60. & 63. In other specimens, on the other hand, the vessel wall is pervaded and, in some instances, almost completely replaced by spaces, which by their confluence have led to the production of fluid cavities of large size. Such a condition is well shown in figures 65,68. As a general rule it may be stated that, in vessels of the same thickness, these structural changes are more evident the nearer the vessels are situated to the developing ovum. It may, also, be laid down as a general rule that in the vessels taken from the same pregnant tube and at the same distance from the ovum, the degree of involvement of their/

their walls in the process is inversely proportional to their thickness. A remarkable and, at the same time, an important reservation must be made, however, in the case of vessels whose walls are the seat of a definite decidual enlargement of the cells. In this case the decidual formation appears to constitute a barrier which prevents the fluid escape to the degree in which it is exhibited by the vessels in which the change is absent. In figures 99-101 are shown sections of vessels presenting a decidua-like formation in their walls, and it is to be seen that the changes described are, if present at all, exhibited only in a comparatively minor degree. These facts, and their relation to the question of the function of decidual cells, will be fully discussed in a subsequent part of this work.

We have already seen that, in the fluid infiltration of the innermost portion of the vessel wall, we are compelled to invoke some explanation other than a mere mechanical separation of the elements forming the wall, or a transudation from a region of higher to one of lower fluid pressure. This conclusion was suggested and substantiated by the changes which are induced by the process in the structure/

structure and position of the endothelial cells. From the detailed description just recorded of the changes as they advance outward to involve the other parts of the vessel it would seem that sufficient has been said to warrant the conclusion that, here again, the same process has been in operation. That the separation and spreading apart of the structures forming the degenerated vessel wall is not due to a merely mechanical influence is strongly indicated by the fact that the results, as evidenced by the histological findings, coincide in every respect with those already noted in connection with the endothelial and immediately sub-endothelial part of the vessel. If further proof of this contention were necessary it is derived from the fact that, here again, the fluid contained in the tracks channelling the vessel wall must be under a tension actually higher than that in existence in the vessel lumen. This is demonstrated by the fact that these fluid spaces or channels are seen to be in direct continuity with similar spaces, in which the fluid has collected under, and led to an inward projection of the endothelial cells. (Plate IX). A demonstration, moreover, of the fact which is furnished by a number of my specimens, namely that the tracks of the oedematous escape, where it leads to a ploughing/

ploughing up of the surrounding tissues is in direct structural continuity with such endothelial spaces, would indicate that in the transference of the fluid from the vessel lumen to the tissues there must be in operation some force of a potent nature. We have already excluded changes in the composition or the pressure of the blood as the causal agent, and we are thus reduced, in our quest after the secret, to some alterations in the tissue activity of the structures of the vessel wall or the surrounding part of the tube.

In some of the vessels still situated at a distance from the actual site of the cellular invasion of the tubal wall by the foetal trophoblast, the process described in the foregoing pages has advanced to the extent of resulting in a wholesale crumbling and solution of the vessel wall and the creation of gaps leading to the establishment of an uninterrupted communication between the vessel lumen and the surrounding tissue spaces. In such cases there is present a wholesale extravasation of blood corpuscles into the perivascular tissues (Figures 58, 59). It is noticeable that this blood escape from the thick-walled vessels has occurred to any considerable degree only in the proximity of those vessels where the/
the/

the fluid infiltration has led to the production of a breach in the vascular wall. There is often detected, however, a certain amount of blood escape into the vessel wall and the surrounding tissues even in the case of those vessels where the teasing asunder has not taken place to this excessive degree. Red cells, singly or in small numbers are often seen lying immediately under a detached endothelium or in the clear tracks which canalise the vessel wall, the endothelium of which is, in some cases, perfectly retained. It sometimes looks as if the red cells have actually passed into the interior of a vacuolated endothelial cell. These appearances suggest strongly that there may be a certain amount of blood escape from the vessel lumen even in the absence of a demonstrable track leading from the interior of the vessel. It would seem obvious that the escape of the more solid constituents of the blood necessitates a certain degree, however small, of separation of the cellular elements of the vessel lining. It is possible, where these are not detectable by the microscope, either that the spaces left are too small to be recognised, or that they have closed in again after the passage of the corpuscles, in a manner something/

something similar to that which is supposed to occur during the process of phagocytosis.

In the case of the thicker-walled vessels how is the complete communication between the lumen and the surrounding tissue finally established? We have been able to follow with a considerable degree of precision the manner in which the sub-endothelial region is brought into communication with the outer tissue spaces. The completion of the process is a little more difficult to understand. In some cases, even at an early stage of the hydropic infiltration of the vessel wall, the endothelial cells are detached from one another or they are seen to be lifted up completely from the underlying tissues. In such vessels the continuation of the process, in the way in which we have described it, will eventually result in the complete detachment of the endothelium and the production of a complete gap in the vessel boundary. In some vessels, however, the endothelium may be retained even at a late stage of the process (Figure 63). How, in such a case does the partition still remaining between vessel lumen and tissue, in the form of the endothelial lining become disposed of? It is obvious that an increase in the tension of the escaping fluid may suffice to completely detach/

detach the endothelial cells. In other cases the degenerative processes which have preceded, or are progressing pari passu with, the other changes in the vessel wall, may determine a softening and disappearance of the endothelial remnants.

That even the comparatively small additional force necessary to displace the fine lamella of vessel wall still persisting is not derived from the intra-vascular tension is suggested by a study of figures ⁶³ and 97 when it is seen that in a part of the vessel wall, which lies immediately adjacent to a region of complete separation, there is still present an inward projection of the fine endothelial layer. However accomplished the establishment of a complete and uninterrupted connection between lumen and tissue, permitting of a wholesale escape of all the constituents of the blood, would seem to be an inevitable consequence of a steadily increasing involvement of the vessel wall by the process which we have described.

From what has been already said it will be easily recognised that the degree in which different vessels, and different parts in the course of the same vessel, exhibit the changes, varies within wide limits. When the condition has progressed beyond the/

the earliest stages, in which only the innermost part is affected, one usually encounters a widespread fluid infiltration of the vessel wall. This may manifest itself in the existence of a large number of small fluid vacuoles or spaces scattered irregularly throughout, or it may, whilst involving the whole wall to some extent, have become more concentrated at one part with the production of almost a complete channelling of the wall (Figure 63). In other cases this condition is present at two or more places, whilst, in still other specimens, there has been a wholesale spreading apart of the structures round the entire vessel circumference (Figure 96). This constitutes the stage which immediately precedes the stage of complete loosening and gaping, associated with an extensive flushing of the surrounding tissues with the liberated blood.

In all my specimens of tubal pregnancy, in which the chorionic cells were found to be well preserved at the time of examination, the changes above recorded were detected in the vessels. The degree in which the tubal wall is involved in the process would seem to be for the most part proportional to the size of the engrafted ovum. The distance along the tube to which the structural alterations have extended is smallest in the youngest specimen/

specimen of the series, and is greatest in the oldest specimen. In one of the older specimens, in which the pregnancy has occurred in the ampullary part of the tube, the softening and dropsical infiltration and detachment of the vessel walls is present to a marked degree even in the thick-walled vessels towards the inner end of the tube. (Figure 96 & Plate XII).

The description of the vascular changes hitherto recorded has more especially dealt with the thicker-walled vessels, in which the more rigid walls have resisted the process to a greater degree than the thin yielding walls of the smaller vessels. This resistance to the influence conspiring to detach the structures of the vessel wall, has, in the case of the thicker vessel, forced, as it were, the process into prominence and has presented to us evidence of a more legible nature in our attempt to decipher the secret underlying the manner in which the growing ovum is furnished with the supply of maternal blood (of menstruation). In regard to the smaller vessels we shall have to study, and endeavour to explain, some rather remarkable changes which they exhibit. In the meantime it may be stated that in the case of these the fluid exudation and/

and blood extravasation have occurred in the same way and are, on the whole, more evident than in the thicker-walled vessels at the same distance from the embryo. (68-71).

It is by the process described that the gross vascular changes in the proximity of the ovum are produced, changes which I referred to at the commencement of this discussion. The softening and separation of the wall with the subsequent increase in the diameter of the vessels in this region would seem to be entirely dependent on changes of this nature. The fact that the process can be traced with accuracy through all the stages, from the dropsical infiltration of the innermost part of the vessel wall up to a complete severance of the constituent elements by the same means, would seem to prove beyond doubt that the gross structural alterations detected in the neighbourhood of the chorionic cells must be attributed to some influence other than a mere mechanical giving-way of softened boundaries before an enhanced blood pressure. The changes present are much more complex and are associated, rather, with some structural alterations, which enable the tissues of the vessel wall or the surrounding/

surrounding area to pass on or imbibe the fluid from the blood. The tissues, in other words, assume an active part in the fluid escape, and are not merely in the condition of a medium exhibiting a passive outward displacement. A recognition of this fact alone suffices to explain the conditions encountered. Dependent, as they must be, on some influence emanating from the growing ovum, the vascular changes are most evident in the proximity of the foetal elements, where this influence, of whatever a nature it may be, is most felt. As this foetal stimulus gradually extends the sphere of its activity, more and more distant regions of the tubal wall come successively under its sway, the changes gradually diminishing in intensity as the region of the ovum is left behind, until ultimately they completely fade away. These facts would suggest that the embryonic influence may be of a chemical nature, perhaps of the order of an enzyme. This point will be discussed more in detail in a subsequent section of this research.

In this place it must be recalled that the exact nature of the process, by which the wholesale gaping of the vessels on the surface of the gestation/

gestation chamber occurs, is, in this region, obscured often to an extent which renders it unrecognisable. This is due to the excessive degree to which, in this region, the degenerative processes have advanced. In this location the vessel walls and the surrounding tissue are often represented by a structureless, fibrinous material, richly sprinkled with blood corpuscles, (Plates VII & VIII) It is interesting, however, to note that traces of the process can be detected even here. The degree of opening up of the vessels bordering on the intervillous space varies from an extensive gaping of the wall to a condition in which there is still left a considerable interval of the degenerating tube between the blood lumen and the intervillous space. Even in the latter case there is seen to be a wholesale exodus of the contained blood into the surrounding tissues with a coincident teasing asunder of the vessel boundaries. The consequence of this is that the vessel, as it were, invades the neighbouring territory and advances to join the large blood track. The penultimate stage of this process is demonstrated in Plate VII where there is left between the lumen of one of the vessels and the blood lake only a fine sheet through which/

which the blood is streaming into the foetal chamber. It is interesting to note that even in this greatly degenerated region of the tube wall there are still present large numbers of well-preserved nuclei, which, in all probability, correspond to connective tissue cells, which resist the degenerative influence to a remarkable degree. In the changes which these cells exhibit there is evidence that they are acting in such a manner as to lead to an imbibition of fluid from the neighbouring blood tracks. This fact will be described in greater detail in a subsequent paragraph.

The process underlying the teasing out of the walls of the maternal vessels, by means of which the growing ovum secures its supply of blood, we have seen is not amenable to a purely mechanical interpretation. It is dependent on a change of greater complexity than a mere giving way of softening walls with a squeezing out of the contained blood fluid and corpuscles. We have likewise adduced evidence to prove the invalidity of the orthodox belief that the necessary blood supply is procured by a destruction and displacement of the vessel walls by the locally invading chorionic cells. If these explanations/

explanations fail to elucidate the factors in operation, what other process must be invoked? Reference to the list of the possible agents responsible for an increased escape of fluid from vessel to tissue, reveals the fact that, having disposed of the blood, our enquiry is now limited in the first place, to the endothelium and, in the next place to all the structures situated external to this.

SIGNIFICANCE OF THE ENDOTHELIAL CHANGES.

Can an altered activity on the part of the endothelial lining of the vessel alone suffice to explain the phenomena present, namely the dropsical infiltration and detachment of the vessel wall? Can a selective or secretory action of the endothelium be entertained as, of itself, an adequate explanation of the changes induced? The structural changes in the endothelial cells which we recorded in a previous section of this investigation might, at first sight, appear to afford an affirmative answer to this question. The process, in its incipient stages, is often associated with a fluid imbibition leading to a distension or vacuolation of the individual lining cells. This change/

change is to be considered, without doubt, as a precursor of the more marked subsequent fluid transferences. Is it to be regarded as bearing a causal or merely an incidental relationship? That the endothelial vacuolation, which is, almost doubtless, associated with the process underlying the oedematous escape, is probably to be looked upon as a degenerating change, would seem to be indicated by the ensuing cell changes which are detected. After a certain degree of distension is attained there occurs a separation of the cell wall with a consequent amalgamation of the cell cavity with that of its neighbour or the fluid space under the endothelium. We have already seen that this disappearance or rupture of the adjacent cell membranes may result in the production of a fluid track continued for a considerable distance along the vessel and representing the running together of the vacuolated cells. In other words, the changes described correspond in every detail, with those found in the so-called Hydropic Degeneration of tissues. The fluid contained in the spaces thus created towards the endothelial aspect of the vessel is under a tension higher than that existing in the vessel interior.

If/

If it be maintained that these changes do not per se contra-indicate the existence of a specific secretory faculty on the part of the endothelial cells, it must, I think, be freely admitted that the force exercised by the escaping fluid, which such an action might transfer from vessel to tissue, must be inadequate to determine the drastic changes present. It is inconceivable that the tension of the fluid, which the cells might secrete, would be alone sufficiently great to lead to the wholesale detachment and teasing out of the structures which occur even in a thick-walled vessel, and at the same time plough up the adjoining tissues.

That the oedematous softening of the vessel walls is not due to an increased endothelial activity, is proved, in addition, by the fact that the changes are present even in the cases where the endothelium has been detached. But, it may be urged, is it not possible that in these vessels the oedematous infiltration, which has been inaugurated by the activity of the endothelium, may, subsequent to its removal, be carried on by a mechanical opening out of the wall by the liberated blood? It may be asserted that now we have lost the clue, in the shape/

shape of the projection of the endothelium into the vessel lumen, which could be explained only by assuming the existence of some cellular or tissue activity causing the fluid escape. This objection, which, at first sight, seems difficult to meet, is easily disposed of by the fact, which we have already noted, that the blood pressure must be considered to provide a factor, which, if not quite negligible, is certainly of minor importance in causing a separation of the elements of the vessel wall. We have already referred to the observation that even in a large sized and thick-walled vessel, where the fluid infiltration of the wall has been associated with a detachment of all the structures save the endothelial layer, the very fine film left behind is sufficient to resist the intra-vascular pressure. This point is well demonstrated in figures 63 and 97. .

That the vacuolation of the endothelial cells is to be looked upon, not as an indication of an activity of cells specially differentiated for a secretory function, but, rather, as a condition merely incidental to the changes which are associated with the oedematous escape, is demonstrated by the discovery of an exactly similar phenomenon in the connective/

connective tissue cells of the vessel wall and the surrounding area of the tube through which they course. This remarkable condition, which has been merely touched on in a preceding section of this investigation, has been intentionally held over for a fuller discussion in the present place.

As already noted the presence of a developing ovum in the tubal wall is associated with a degeneration of the muscular fibres. This is most evident in the immediate vicinity of the foetal structures and is, on the whole, the more wide-spread throughout the tubal wall, the older the embryo. In its earliest stages these changes consist in a swelling of the substance and nuclei of the fibres with a coincident diminution in their staining powers. With an advance of the process, the cell boundaries become obscured and ultimately lost and the fibres fuse with one another to form a structureless fibrinous material. Pari passu with these changes there is a progressive disintegration and ultimate disappearance of the nuclei. These degenerative alterations, though, by no means, confined to the proximity of the foetal elements, are here most evident. In some cases the uniformly stained, degenerated/

degenerated material on section exhibits under the microscope an appearance strongly suggestive of opaque glass. In my sections, these are the muscular changes invariably present; in none, even the youngest, is there any evidence of a muscular hypertrophy such as is found in the uterus during pregnancy.

CHANGES IN THE CONNECTIVE TISSUE CELLS.

In marked contrast with these changes in the muscle is the condition of the connective tissue cells of the tubal wall. As has been already mentioned, scattered irregularly throughout the tube wall, the connective tissue cells have enlarged in a manner closely resembling the decidual increase in the stroma cells of the uterine mucous membrane. Even where this alteration has not occurred to such a definite extent, the connective tissue cells are, however, for the most part somewhat enlarged. But, what is even more characteristically detected, is the fact that the nuclei have preserved their structural appearances and staining properties, sometimes/

sometimes to a degree almost complete, and this
even in these regions where the muscular disintegration
has occurred to the most marked degree. This observation which I have been able to note in all my specimens, which are sufficiently well preserved for a satisfactory histological study, would indicate that, in their re-action to the foetal cells, whatever this may be, the two main structural constituents of the tube wall, namely the muscle cell and connective tissue cell, exhibit markedly varying degrees of resistance. Whilst the former quickly undergoes a progressive disintegration and ultimately becomes unrecognisable as such, the latter tends to persist and often preserves its identity throughout. In figure 53 are seen vessels embedded in a medium composed of degenerated muscle; the surrounding connective cells are seen to be wonderfully well preserved.

But there is, in relation to the connective tissue cells, another fact of great importance, and one which especially interests us at present in our endeavour to show that the histological changes, which we encountered in the endothelial cells, are not to be looked upon as indicating changes necessarily dependent on a specific secretory function./

function. This fact is found in the observation that the fluid imbibition and swelling of the cells lining the vessels to which attention was directed on a preceding page, are exhibited in precisely a similar way by the connective tissue elements. In all my specimens there is evident a marked degree of fluid imbibition by and distension of the connective tissue cells in the tubal wall. In some sections this condition is exhibited by the majority of these cells, in other regions it is present only to a minor degree. It is invariably detected in the connective tissue cells in the proximity of the ovum, where the tissues are markedly infiltrated with a fluid exudate; so also in the oedematous tracks round and in the walls of softening vessels. Even in the extremely degenerated structures immediately bordering on the intervillous space the process is often well marked. It is always visible throughout the tube at a long distance from the foetal structures.

The description of the process as detected in the endothelial cells applies with equal force to the changes exhibited in the connective tissue cells. The affected cell becomes swollen up with a clear fluid, the cell substance becoming displaced/

displaced to the periphery of the cell, often as a fine film, which, in well preserved specimens, is often easily seen. The appearances produced by the cellular changes are many and various. The vacuoles may be small or large. In the former case the cell substance is seen as a distinct envelope round the imbibed fluid, in the latter case the cytoplasm may be represented by a mere film, which in some cases has disappeared and the remaining portion of the cell or perhaps only the nucleus, appears to lie in a clear space in the tissue (Figures 74, 75, 76). In some cases the resulting appearances might warrant the idea that the clear spaces have been produced by a shrinkage of the cells contained and that, in reality, the changes described are not dependent on an intra-cellular fluid collection. That this, however, is not the true explanation of the changes is proved without doubt, by the observation that it is often easy to trace, as already mentioned, the cell substance, as a complete envelope round the vacuole. Another appearance of interest and one which proves beyond cavil that the changes depicted are due to a fluid distension of the cell is seen in the fact, which we noted in connection with the changes exhibited by the endothelial cells, that the chromatin substance/

substance of the nucleus is often observed to be stretched round the intra-cellular accumulation sometimes being drawn out as fine strands extending round a large part of the cell circumference.

The fluid vacuoles are, for the most part, chiefly disposed and reach their largest size in the neighbourhood of the nucleus. Where the connective tissue cells are drawn out, and this is the shape mostly assumed by the altered cells the vacuolation, however, may be present at any part of the cell substance, even at a distance from the nucleus

(Figure 74). This may be encountered even in the fine filaments into which the cell substance is frequently drawn out. In these

cases the appearance produced is that of a beadlike swelling in the course of the cell. In such cases the main portion of the cell protoplasm is usually involved in the process. In other cases the entire, or the greater part of the length, of such an elongated connective tissue cell is occupied by a drawn out, clear fluid track (Figure 76). In many cases it is easy to trace such a track without interruption into a corresponding space in an adjoining cell. The rationale of this is easily understood by/

by the fact that the connective tissue cells are intimately connected, by means of protoplasmic out-runners from their bodies, with adjacent cells. This permits of the establishment by the fusion of vacuoles which develop in the intervening cell bridge, of a continuous fluid track extending from cell to cell. In some cases it is possible, in the same section, to trace such a canal through three, four or even more cells. Where cells lie side by side, with their long axes more or less parallel, there may be a disappearance of the intervening cell walls, with the production of a fluid space lined by two cells. (Plate XI). This process may continue until ultimately a large oedematous space is formed which is lined by a considerable number of cells. This process is easy to detect; its importance will be more fully related when we come to investigate the manner in which the sinus-like blood spaces are formed. When the vacuole of the cell reaches any size it is usual to find that the nucleus is drawn out and elongated in the direction of the long axis of the vacuole.

On Figures 76 and Plates X, XI are shown a few of the variagated changes in contour, some of them very bizarre in nature, which the cells may/

may present as the result of this vacuolated condition. Many of the appearances are artificial and are due to the direction in which the section has been carried across the cell. For example, where the cell is cut across transversely through the level of the nucleus, the well known "signet ring appearance" is produced. At one pole is the nucleus and extending round, and enclosing the fluid, there is the attenuated film formed of the displaced cell protoplasm. Again, where the vacuolated cell is cut across obliquely, the cell substance may appear to project as two horns from the end of the cell, which pass completely or only partly, round the clear space. In this case we obtain the appearance often seen in the typical fibroblast (Plates X and XI). In the vacuolated spaces of the connective tissue cells, it is often possible to detect red blood corpuscles. This fact will be more specially referred to in a section devoted to the description of new vessel formation as seen in the pregnant tube.

We have thus seen that the process of fluid imbibition, which is presented by the endothelial cells, is exhibited in a manner almost precisely identical, /

identical, by the connective tissue cells of the tube wall. The appearances in each case correspond to the process of Hydropic Degeneration as seen in other tissues of the body.

We have seen that the fluid accumulation in the vessel walls, which usually commences on the internal aspect, and which, by its increase, ultimately results in a complete severance of the vessel confines, is determined by some tissue alteration which leads to an active fluid imbibition. The oedematous collection occurs under a hydrostatic pressure higher than that exerted by the blood against the vessel wall, and is so considerable as to lead, in many instances, to a detachment and projection into the vessel lumen of the inner layer or layers of the vessel wall. In the earliest stage it is represented by a fluid distension of the endothelial cells. The fluid thus confined within the individual cells soon bursts its bounds and escapes, first into the next portion of the vessel wall, and thence through the succeeding layers till it ultimately reaches the surrounding tissues which become ploughed up in the process. In the involvement of the vessel wall, the process may be represented by the fluid spaces/

spaces in the extra-cellular tissue, or it may, as in the endothelial layer, be represented by a hydropic accumulation actually in the connective tissue cells. (Figure 23)

The same applies to the surrounding tissues. When the loosening of the vessel wall has occurred to the extent of creating a complete breach in its continuity, and in the case of the thicker vessels, at any rate, not till then, we have an escape of the corpuscular elements of the blood into the surrounding tissues. It is important to note that, although in the smaller vessels there may be the occurrence of an extensive perivascular haemorrhage before the surrounding tissues have been seriously involved in the oedematous escape, in the thick-walled vessels, on the other hand, there usually occurs a wholesale displacement of the surrounding tissues by a watery discharge before the blood cells leak out. In some cases the vessel may lie in a large clear space, formed by a wholesale displacement of the surrounding tubal tissues, and yet the loosening of the vessel wall has not taken place to the degree necessary before there can occur an escape of the red cells. (Figure 96).

We thus observe that the amount of the fluid escape varies within very wide limits. We have/

have noted that in the vessel wall and in the surrounding tissues it may be represented by small, clear spaces. From the smallest fluid accumulation we can distinguish all grades up to the very largest oedematous tracks in the tubal wall. It may be stated as a general law that in the same tube the fluid exodus is greatest in the immediate vicinity of the ovum. In different tubes, also, the condition is greater, the greater the age of the ovum which is imbedded in the tubal wall.

To resume the argument, we have been enabled, as the result of the study of the histological changes present in the vessels and the tissues of the pregnant tube, to dispose, in the first place, of a direct, cellular trophoblastic invasion and, in the second place, of a softening and mechanical filtration or a mere passive displacement as explanations of the manner in which the vessel walls become teased out and ultimately completely detached, permitting of a free escape of the contained blood into the surrounding tissue spaces, or, in the case of the vessels immediately apposed to the gestation sac, into the intervillous space. We were then able to discover that a "vital" or secretory fluid transmission on the part of the endothelial cells fails to explain all the phenomena, and we were reduced, in/

in our quest after the secret, to tissue changes as the only possible solution of the problem. We have seen that the fluid is drawn into the tissues where it accumulates under a tension greater than that in existence in the corresponding blood vessel. The tissue changes induced coincide with these which we associate with Hydropic Degeneration elsewhere.

SIGNIFICANCE OF TISSUE CHANGES IN THE PRODUCTION OF THE OEDEMA AND THE HAEMORRHAGE.

What conditions determine the accumulation of fluid in a cell or in tissues under a tension greater than is attributable to a mere passive escape from the neighbouring blood tracks, from which the fluid is derived? If we turn for assistance in answering such a question to a modern text-book of pathology we shall gain some information of importance. Adami (The Principles of Pathology, Vol. I, 1909) defines Hydropic Degeneration as "the appearance of definite vacuoles in the cytoplasm, containing a watery fluid, which vacuoles may attain so great a size that the cell undergoing disorganisation bursts, and, with its neighbours, becomes represented by/

by a vesicle visible to the naked eye". In this description of the process we recognise a close resemblance to the changes which we have noted in the vessels and tissues of the pregnant tube. Adami goes on to say that "This rapid imbibition and accumulation in a cell can, upon physical grounds, have only one explanation. The constitution of cytoplasmic matter, as also of the nucleus, is colloidal, and colloidal membranes (for such we can regard the surface layers of cells) have characteristic properties. They hinder the diffusion of crystalloid molecules to a considerable extent. Although animal cells possess no well-formed outer membrane (as do plant cells) we are led to believe that in animal cells a fine layer of similar nature acts physiologically as such a membrane. We, therefore, conclude that the essential cause of hydropic degeneration is some dissociation of the complex colloid material of the cytoplasm, whereby, either by cleavage or ionisation, crystalloid bodies make their appearance in the protoplasm. As an illustration of conversions of this order, it may be noted that the peptones, leucin, tyrosin etc., which are the products of the breaking down of (colloidal) proteins, are of distinctly crystalloidal nature. So/

So long as such products are present within the cell body in greater concentration than they exist in the surrounding medium, there will be tendency to osmotic diffusion inward of watery fluid until such time as the osmotic pressure on the two sides of the membrane becomes equal. In other words, the cell swells up and becomes hydropic."

If the conclusion to which our investigations have carried us be correct, and I maintain that no other explanation accords with the ascertained facts, we must look to some protoplasmic change similar in nature to that which is described in the above passage for the key with which to unlock the secret of the fluid transference from vessel to tissue, as it is encountered in the pregnant tube. By this means, and by this means alone, can we satisfactorily explain the fluid imbibition and distension of the endothelial cells and of the connective tissue cells, the first of which we invariably detect and the latter whenever the tissue destruction is not too extensive. By this means, we procure, further, an explanation of the fluid accumulations so richly scattered through the affected tube, where the condition is distinctly due to a bursting of the walls and amalgamation of such distended/

distended cells. Does this factor, namely an osmotic diffusion from a place of lower, to one of higher crystalloidal concentration, amply account for the fluid accumulations which so far as we can see are purely extra-cellular in their position and which in some instances attain huge dimensions? Such a fluid collection we have described as frequently, especially in the early stage of the oedematous teasing out of the walls of a well supported vessel, leading to a wholesale floating-up and projection into the lumen of the endothelial sheet. This condition is found especially in those vessels where the immediately adjacent portion is wholly, or only slightly involved in the process. The change in such a case, whilst in all probability initiated by an active accumulation in the individual endothelial cells, must, by the time it has reached this stage, be due to an oedematous collection, for the greater part, completely external to the cells and not to an amalgamation of a large number of cells each exhibiting the change. What these appearances teach us is, that the osmotic transference of fluid can lead to the production of, and can occur into large spaces created in the tissues without the intervention of obvious cellular changes. In this case the/

the colloidal membrane necessary for the process has been furnished by the endothelial sheet. The only possible interpretation of the phenomena, then, is that into the tissues concerned there has occurred the passage of crystalloids which raise the osmotic pressure and determine the diffusion of the fluid across the endothelial layer into the sub-endothelial region. As we have repeatedly noted, this structural alteration in the vessel wall is rarely limited to its endothelial aspect. In most cases it is quickly followed by a similar oedematous accumulation into the immediately external part of the wall, which in many instances, is separated by a fine tissue partition from the inner fluid distended space. This film of tissue intervening between the two dropsical cavities, which, in many cases, is in the pregnant tube nothing more than a greatly degenerated portion of the vessel wall, appears to act, like the better preserved endothelial sheet, in the capacity of a colloidal membrane, which, while retaining the crystalloids, determines the diffusion of fluid from one space to the other. In such a case, again, the process would seem to have occurred without the medium of an actual intracellular accumulation. The tissues themselves/

themselves are charged with crystalloids which lead to an elevation in the osmotic tension. In this case we have again to deal with a passage of fluid from one region of lower to another of greater osmotic pressure. And so on the process extends till, even in the case of a thick-walled vessel, the entire wall becomes teased out, and the surrounding tissues become directly involved. That an explanation of this nature, namely a continual osmotic stream from a location of lower, to one of higher crystalloidal concentration, must be the true one is evidenced by the fact that where the tracks thus successively created become continuous by a disappearance of the intervening colloidal partitions the contained fluid is seen to be under a tension in excess of that exerted by the lateral pressure of the blood in the corresponding vessel. This fact we have conclusively demonstrated in a preceding part of this research.

The manner in which the colloidal partitions give way is intimately bound up with one of the most characteristic vessel and tissue changes detected in the pregnant tube. We have already observed that in addition to mere displacement of tissue there has occurred in many places a marked solution of/

of tissues. This especially involves the degenerating muscle, in which one can often see a wholesale disappearance of the muscle fibres, which apparently become transformed en masse into soluble ingredients which pass into solution in the fluid absorbed.

The fluid escape from the vessels does not always follow on lines associated with such gross microscopic changes as those described above. In Plate IX is represented a fine walled vessel from which there is occurring this dropsical infiltration. On the inner aspect we see the hydropic changes in the endothelium, to which we have frequently referred. The fluid imbibition has here and there round the vessel circumference led to a detachment and bulging of several of the lining cells towards the lumen. The underlying fluid accumulation is well seen on the lower aspect of the plate. That this has been formed by an osmotic diffusion through the endothelial sheet must, I think, be freely admitted. Besides the definite evidences of the osmotic interchange as demonstrated by the endothelial vacuolation and the sub-endothelial spaces the immediately subjacent part of the tube, which, in this case is formed, not by the structures of the vessel, which is possessed of only an endothelial layer, but by the tissues of the tubal wall, is seen to be thickly studded with clear spaces/

spaces of varying size. The fact that these spaces can often and with ease be traced directly into the sub-endothelial region proves beyond a doubt that their contained fluid has accumulated under a tension considerably greater than that of the intra-vascular pressure. In other words we learn that the passage of the fluid into the tissues of the tubal wall is established by a process of imbibition and must be dependent, as before, on some tissue changes. The exact nature of these changes is still beyond our grasp, but from their effects we must assume that they are associated with a liberation of crystalloids by means of which there ensues an elevation of the osmotic pressure of the tissues.

The giving way of the tissue partitions between the fluids in two spaces formed in the above-mentioned way, may be explained by purely mechanical influences. As can easily be understood, the fluid in its passage across the membrane may accumulate in one of the cavities to such an extent as to thin out and rupture the intervening septum. When this occurs the osmotic stream between the two regions must, of necessity, cease. Into the common space thus produced, in which the crystalloidal content may/

may be still high, there may, however, be further diffusion of fluid from a region of greater dilution e.g. the blood. Whilst such a mechanism would furnish an explanation of the disappearance of the intervening septum it is possible that the real explanation is to be found in the structural nature of the partition. This is not, as in the case of the colloidal membrane employed in experimental research, a structure which remains unchanged except for the mechanical displacement which it exhibits when the tension on one side exceeds that on the other, and which, when this pressure discrepancy is sufficiently great, might be conceived to rupture. In the case at present under discussion, we are dealing with a tissue which can itself become teased out and disappear in response to the same process which has determined the fluid transference through it. If we can assume, which I think is not unreasonable, that the tissues within a small area are charged to a like degree with crystalloids liberated by protoplasmic changes induced by the chorionic activity, we can see that a continual passage of fluid from lower to higher osmotic levels is efficiently maintained until the tissues are saturated. For the portion first involved by the fluid ingress falls in osmotic pressure in/

in proportion to the amount of fluid entering and this establishes a pressure discrepancy between it and the adjacent tissues which determines a diffusion across the colloidal membrane and so on till large oedematous areas are produced. The fluid tracks thus produced gradually, and more or less uniformly, widen their circumference, the increasing fluid necessary for the process being derived from the blood stream, which is depleted to a corresponding extent.

As we have seen the above process results, in many cases, in a wholesale opening out of the structures forming the vessel wall, and this, even in those cases, where this is thick and well-supported. Whilst these changes are most manifest in the vicinity of the chorionic structures they are nevertheless still evident, and in the case of the older embryos, often to a marked degree, at a distance from the ovum bed. In one case the changes were detected in large thick-walled vessels towards the inner end of the tube which contained a growing ovum in the ampullary portion. For an escape of the corpuscular elements of the blood into the vessel wall and thence into the neighbouring tissues a complete and continuous channel connecting vessel lumen and tissue spaces/

spaces is essential. The mode in which the exodus of the solid constituents of the blood is carried out will be discussed more fully in a later section.

The description of the manner in which the dropsical infiltration of the vessel walls occurs applies with equal force to the way in which the tissues become opened out, sometimes to the extent of creating large oedematous tracks. It is often possible to recognise, before the inner part of the vessel walls have given way, that the fluid which has thus accumulated in the tissues is under a pressure greater than in existence in the vessel lumen. This is demonstrated by the fact that we are able to trace, in many cases, a continued track leading from an unbroken endothelial layer, which has been bulged towards the vessel lumen, through the vessel wall and thence into the surrounding affected tissues. To my mind this observation is amenable to one explanation and to one explanation only, namely that the fluid has escaped, not by a mechanical transudation through the vessel wall, but by an alteration in the tissues themselves of a nature which determines an increase in the osmotic tension and an osmotic diffusion through the vessel walls. This, in all likelihood, is, as in the case of the vessel walls, dependent on a change/

change in the protoplasm of the tissue cells which results in a liberation of crystalloids. It seems to me, in addition, that the displacement of tissue, which occurs in the tube during pregnancy is too extreme in degree to be attributed to a mere mechanical infiltration of fluid through the vessel walls. It is often possible to recognise a wholesale displacement and separation of the muscular tissue of the tube wall even when the bundles exhibit little evidence of degenerative softening. The fact, moreover, that even where the process has resulted in a complete teasing apart of the vessel wall, the fine, endothelial pellicle may remain perfectly intact, would tend to indicate that intra-vascular pressure plays a very unimportant part in the production of the changes encountered. In the case of the vessel where there is produced clear tracks from endothelium to tissue the osmotic flow may have been a gradual one, first through vessel wall with a successive detachment and separation of the tissues, which have in their turn acted the rôle of colloidal membranes, until ultimately the fluid, still diffusing into realms of increasingly high osmotic tension reaches the surrounding tissues, where the same process proceeds. Here it may/

may progress to the extent of completely separating the vessel from the neighbouring structures. This, as has already been mentioned, is rendered the easier by the softening and degeneration of the tissues which occurs in the pregnant state. In fact, as will subsequently be pointed out it is, in all probability, the degenerative changes in the tissue protoplasm which results in the liberation of the crystalloids and thence determines the occurrence of the phenomena.

Whilst it is easy to trace the various steps in the process just described by which the osmotic stream traverses the vessel wall in its passage to the tissues, it would seem that this description does not embrace all the facts. In the above-noted process it was observed that the fluid leaks by well-defined stages through the vessel wall, each part of which after assuming in its turn the function of the colloidal membrane gives way and a track is thus produced by the gradual teasing out of the wall, which conveys the fluid to the tissue. This channel may be complete or it may be interrupted by parts of the vessel wall which persist. In other cases, however, there may be a wholesale escape of fluid through a vessel which exhibits the above changes/

changes in only a very small degree or not at all. In such a condition, which is usually associated with a well supported wall the structures of which are too closely knit together to become detached in the above manner, the entire thickness of the wall has functioned as the colloidal membrane, separating the fluid of comparatively low osmotic tension (the blood) from the regions of high crystalloidal concentration. In such a case the conditions, although identical in their fundamental nature with the above-mentioned process, conform more closely to the conditions in which the phenomena of osmosis are studied in vitro, the thick-walled vessel in this case corresponding to the animal membrane employed for the experiments.

In the above description of the phenomena which are detected in the pregnant tube, an attempt is made to indicate that the true explanation of the fluid transference, and the changes which this induces, must be dependent on alterations in the normal osmotic conditions present in the tubal wall. It will be noted that our interpretation of the phenomena has been necessarily proscribed within the limits defined by the most recent investigations into the laws of osmosis and diffusion. I contend that the facts/

facts acquired demand, and are only embraced by, an explanation of such a nature. It seems not unlikely, however, that with an increase in our knowledge concerning the laws of osmosis as they apply to the living tissue, the explanation advanced above will require some, and in all probability, considerable re-adjustment. More recent research would tend to indicate that the conception, which we have derived from experimental investigations, that osmosis consists in the diffusion of fluid across a definite and unchanging colloidal membrane into a space containing a simple solution of crystalloids, must be modified when applied to living matter. In a recent article on the "Equilibrium of Colloid and Crystalloid in Living Cells", Benjamin Moore⁽¹⁴⁾ says:-

"The whole chemical structure of the cell and that part of it which is physiologically active is the osmotic machine, and needs no membrane permeable or impermeable in order to exhibit the usual osmotic phenomena of shrinking or swelling, leading finally to disruption in all cases the nature of the bioplasm is so differentiated chemically as to form a dividing surface readily permeable to the solvent, and this is all that is required, in addition/

addition to the varying unions or holding powers between the cell colloids and crystalloids, to establish an osmotic cell. As an example of what is meant here we may instance the swelling of fibrin, connective tissue, and gelatine under the imbibition of water. Between gelatine and water there is no structural membrane with semi-permeable pores, yet the gelatine takes in water in a truly osmotic fashion, and the pressure developed, if the swelling and uptake of water are resisted, is very high". If instead of the idea which demands the existence of a definite colloidal membrane "we take the view, which is supported by experimental facts, that the bioplasm holds the crystalloids in loose union in the cell, so that they cannot for the time escape or diffuse out, and yet admits of a degree of molecular freedom to the crystalloids, so that they still attract water molecules by residual affinity, then we arrive at a conception which is capable of linking together the osmotic properties of the cell, not merely in a statical but in a dynamic way, and gives a basis for understanding the variations in osmotic effects which accompany cell activities from one phase to another". Such an interpretation is essential to explain/

explain on a physical basis the phenomena of secretion and excretion, in each of which osmosis and diffusion play a prominent part. The vague terms in which the above attempted description of the phenomena is couched, although leaving no room for doubt that in the activities of cell protoplasm osmotic influences take a prominent share, yet indicate that we must trust to the further work of investigators on the subject to furnish us with the key to the problems concerned.

One point especially demands further study, namely the exact manner in which the osmotic relations of the tissues are altered by degenerative changes in the cell protoplasm, such as that induced throughout a large extent of the tubal wall in the case of a pregnancy in that region. Whilst we have seen that, in many places, osmotic phenomena as seen in the fluid imbibition and distension of the cells accord with the well known effects of this process in other regions, we have been compelled to introduce a similar explanation to meet the changes induced in the parts of the wall where the cellular characters are lost, and where the tissues are in many instances, represented by a homogeneous fibrinous material. It would seem not unlikely that, under the chorionic/

chorionic influence, the degenerative changes exhibited by the more susceptible elements of the tubal wall, and this as we have seen, applies to the muscular tissue, have been associated with a liberation of crystalloids in a way differing, not so much in nature as in degree, from the more resistant endothelial and connective tissue elements, in which we have seen that osmotic phenomena have entered chiefly in the production of the changes to which they are subject. In a subsequent section of this research devoted to the study of the changes induced in the wall of the uterus by chorion-epitheliomatous masses I shall demonstrate that in the degenerating muscular tissue there is indisputable evidence of an active fluid imbibition such as probably occurs in the pregnant tube. (Plate XVII). We have seen that throughout the pregnant tube the endothelial and the connective tissue cells are greedily imbibing fluid from the blood tracks, and this last observation would indicate that the only other structural element of importance, namely the muscle, is in all likelihood undergoing the same change.

In this connection it is interesting to note that recent research into the activities of the placenta would seem to have demonstrated the existence amongst others, of a proteolytic ferment, which leads to/

to the conversion of proteins to peptones. The importance of this in relation to the present research is that we have an experimental explanation of the changes in the tissues which our study of histological alterations has led us to adduce. This is found in the fact that the digestion of proteins results in a production of substances (peptones etc.) with an enhanced osmotic tension. Be this as it may, however, of one thing our researches leave us confident namely that to fully explain the way in which the vascular walls become teased asunder and ultimately gape, permitting, in the first place an escape of the watery constituents, and, in the second place of the corpuscular elements of the blood, we have perforce to recognise a wide-spread elevation in the osmotic tension of the tissues.

EXPLANATION OF THE BLOOD ESCAPE FROM THE VESSELS.

We have seen that an alteration in the tissue constitution and activity have, by leading to a liberation of crystalloidal elements determined the occurrence/

occurrence of an osmotic stream of the fluid part of the blood through the vessel walls and into the neighbouring structures, a stream which often takes place to the extent of ploughing up large tracts of the tubal wall. We have indicated that the teasing apart of the vascular walls often, especially in the neighbourhood of the chorionic structures, results in the production of a breach or wholesale gaping through which there ensues an escape of the blood corpuscles. This change, we have also noted, is readily discovered in the wall of the pregnant tube, even at a considerable distance from the ovum. In the proximity of the gestation sac this process is, as we have seen, in all probability responsible for the opening of the maternal vessels into the intervillous space and the provision of a necessary blood supply for a developing foetus. Whilst most marked in the case of the smaller vessels, the blood escape thus induced is, however, often detected in the thick-walled vessels. In different parts of the same tube, like the dropsical infiltration, it is, on the whole, in amount inversely proportional to the distance from the site of the embryo. In different tubes, again, the degree in which the haemorrhage is encountered is, for the most part, proportional to the age of the ovum.

The/

The mode in which the blood escape occurs is easily understood by recalling the way in which the oedematous infiltration results in a detachment of the structures forming the vessel walls. As we have seen this often occurs to the extent of producing a direct communication between vessel lumen and tissue spaces, along which these red blood corpuscles are streaming. If the process involves the entire circumference of the vessel wall, as is frequently the case in the immediate proximity of the intervillous space, there occurs a wholesale haemorrhage into the surrounding tissues, the corpuscles streaming out in all directions (Plates VII & VIII). The exact manner in which this occurs is not difficult to understand in view of the previously recorded observations. On Plate IX. is shown a vessel at a little distance from the foetal elements, through the walls of which there is occurring a passage of fluid from lumen to tissue in the manner described in the preceding pages. This is occurring round the entire circumference of the vessel and has led to the production, in the wall and in the surrounding tissues, of fluid spaces and tracks. The vessel cavity ~~is~~ still shut off by the presence of the uplifted endothelial layer. It is clear/

clear that the removal of this (and how this probably occurs I have already indicated) would result in a passage out of the red cells. If the fluid is still being drawn into the tissues by the osmotic changes, it is obvious that the red corpuscles will be dragged out just so far as the process of disintegration has led to the creation of an uninterrupted tissue track. That this does actually occur is demonstrated by the discovery in the nearer proximity of the ovum of the corpuscular elements streaming into these tissue spaces.

Whilst it is easy to understand, in this way, the rationale of the blood escape into the immediate proximity of the vessels, what factors are responsible for the transference of the blood elements into more distant regions of the tubal wall? As has already been mentioned, it is often possible to detect, especially in the neighbourhood of the ovum, a track of haemorrhage extending through the tubal wall for a long distance from a vessel. (Plate VIII.) There would seem to be two possible explanations of the manner in which this blood stream takes place. In the first place it is possible that, subsequent to the teasing out of the tissues with the establishment of a continuous track leading from the vessel interior, /

interior, the stream is determined by the force which is responsible for the flow along the vessel under ordinary circumstances. In addition to this vis a tergo, however, it would seem highly probable that there enters into the process a vis a fronte, in the shape of the tissue changes which, as we have learnt, are drawing on the fluid from regions of lower to regions of higher osmotic pressure. The relative importance of these two factors we are unable to determine with accuracy, though it would seem highly probable, from the researches recorded in the preceding pages, that the latter factor, namely that dependent on the increase in the osmotic tension of the tissues, must assume a part of not inconsiderable importance. On the other hand, it is clear that, whilst it is feasible to imagine that this force might alone carry the blood to the surface of the foetal chamber, for the completion of the process, namely a flowing of the blood into the intervillous space, the first factor would seem to be essential. Though this is the case I shall subsequently adduce evidence in favour of the idea that the fluid absorption by the foetal structures may to some extent aid in drawing the blood through the superficial maternal tissues.

We/

We have repeatedly referred to the fact that whilst these vascular changes are exhibited in varying degrees throughout the wall of the pregnant tube, that portion which borders on the gestation sac is almost invariably seen to be extensively infiltrated with red corpuscles which are seen to be escaping in large numbers through the walls of vessels in this region which have not yet completely given way.

(Plates VII and VIII) Another fact of considerable interest and importance which is observed in this region is that the walls of the vessels concerned are often seen to be most involved in the process on that aspect which faces towards the surface of the foetal advance and whilst the chorionic cells are still at a considerable distance. These facts coincide with what I have previously referred to, namely that the extent to which the vessels are involved reaches its maximum in the foetal neighbourhood, and they, moreover, tend to indicate, what we should expect, that the tissue changes induced by the growing ovum are of such a nature as to determine in the region of the intervillous space a flow of the constituents of the blood towards the region of the chorionic advance. If our interpretation of the phenomena, /

phenomena, then, be correct, we are furnished with evidence which justifies the conclusion that the object of the complex vessel and tissue changes which we have studied in the preceding pages is the provision of a liberal supply of maternal blood for the engrafted ovum.

SIGNIFICANCE OF A DIRECT INFILTRATION OF
THE VESSEL WALLS BY THE CHORIONIC CELLS.

The investigations recorded in the preceding pages have indicated that the orthodox conception regarding the manner in which the blood supply of the foetus is obtained must be modified. There is in action some process other than an invasion and destruction of the vessel wall with a mechanical liberation of the contained blood. That this is not essential to the process is strikingly demonstrated by the fact, which I have described, that the blood can often be seen streaming from the vessel towards the intervillous space when the foetal cells are still at a considerable distance.

On the other hand it is often possible to detect a direct infiltration and destruction of the vessel by the engrafted cells. What is the significance/

significance of this? Such a vessel is represented in Figure 54,55. At one part a villus is seen incorporated with the vessel wall, the tissue of which has been to a large extent removed. Some of the chorionic cells have extended as far as the endothelial layer. The wall in the neighbourhood is cedematous and is infiltrated with blood. The muscular tissue is disintegrated and has, for the most part, disappeared, apparently having entered into a state of solution. It is obvious that here the changes are identical in nature with those seen at a distance from the foetal cells. The difference is one of degree only, being more marked here because of the proximity of the cells. In another part of the vessel wall (towards the left in the figure) there is seen to be a greater destruction and there is seen to have been produced a distinct communication between vessel and intervillous space at the side of the invading villus. Here the tissue removed is, as is often noted, in bulk greater than the chorionic mass; this is clearly dependent on the solving process to which I have repeatedly referred.

The appearances produced, therefore, correspond accurately with those encountered throughout the marginal area of the ovum bed. The corrosion of/

of the vessel walls, by the direct chorionic invasion, is to be looked upon not as the essential factor in the liberation of the maternal blood but rather as an incident in the process by which the tubal wall is uniformly involved. So far from its being correct to state that the blood cannot escape till the chorionic cells directly invade the vessel wall, the reverse is the case. The chorionic cells are actually seen to be burrowing through the tissue towards the vessel from which the blood is already escaping. In so doing they would seem to be developing most in that direction from which their nutrition is flowing. If our interpretation of the process be correct, then, we are in this region brought face to face with a remarkable cycle of events. The chorionic influence (enzyme?) passes into the tissues which become chemically altered and respond by actively imbibing the blood (fluid and corpuscles). This will tend to pass in the direction of the greatest tissue change, i.e. towards the foetal cells and this tendency will be assisted by the active fluid absorption on the part of the foetal elements. These naturally develop most on that aspect facing the direction of the nutritional flow and therefore, grow towards the vessel, the walls of which they ultimately reach, with the/

the results I have recorded. In Figure 54 it is seen that the vessel wall is becoming teased out on the side most distant from the chorionic invasion, a condition which affords conclusive proof of the statements I have made.

The passage of the blood towards the chorionic cells is also facilitated by the vascular expansion which is occurring. This, it is easily seen, must tend to transport the blood en masse towards the chorionic site (Plate VII and Figure 77).

Whilst in the neighbourhood of the chorionic cells the destructive changes dominate the process, this is by no means invariably the case. Whilst the muscle early disintegrates there is often, as I have mentioned, a persistence of the endothelial and connective tissue elements. Not only so, but there may actually be found evidence of a definite re-action in the elements in the shape of a new formation of blood vessels. This obviously will serve the purpose of conveying the blood in the direction in which it is required (Figure 78 .). This again, as I shall show, is merely an evidence of the tissue changes referred to.

S U M M A R Y.

1. The commonly accepted idea that the maternal vessels are opened up by a direct infiltration of the chorionic cells does not suffice to explain all the phenomena.
2. The explanation, also, advanced by one or two investigators, to the effect that the opening of the maternal vessels is due to a giving way before the intravascular tension of the walls of the vessels in the proximity of the intervillous space, which have previously undergone a degenerative softening, likewise fails to embrace all the facts.
3. The investigations recorded here demonstrate that
 - (a) the loosening of the vessel walls is, for the most part, co-extensive in location with the region of oedematous infiltration of the tubal wall. Whilst most evident in the neighbourhood of the growing ovum, these two appearances, the oedematous escape and the teasing out of the vessel walls, are still, however, seen at a distance, sometimes considerable, from the embryonic structures.

(b)/

- (b) The cause of the opening out of the vessel walls is a gradual separation and giving way of the tissues by the dropsical exudate. This, in the majority of cases, commences on the inner aspect of the wall and steadily progresses in an outward direction. In its most marked degree it results in a complete detachment of the wall and a wholesale escape of blood into the surrounding tissues or the intervillous space.
- (c) The changes are manifest even in the thick-walled vessels, especially the veins.
- (d) The oedematous escape determining the changes is not due to a mechanical displacement or filtration. Nor is it due to a secretory activity on the part of the endothelial cells. It is due to some tissue changes which lead to an active imbibition of fluid from the blood lumen.
- (e) These changes must be due to katabolic protoplasmic changes which are associated with the liberation of crystalloids and an increase in the osmotic tension of the tissues./

tissues. By the osmotic diffusion we have the transference of fluid into and through the vessel walls, leading to a ploughing-up of the surrounding tissues to a marked degree.

- (f) The "suction" of fluid into the surrounding region thus produced is associated, in the case of the vessels where there is the creation of a complete breach in the wall, with a passage of blood into the surrounding tissues or into the intervillous space.

MODE OF FORMATION OF BLOOD SINUSES
IN TUBAL WALL.

As has been mentioned in the course of the previous record there is found scattered about the wall of the pregnant tube, a considerable number of large, thin-walled blood spaces or Sinuses. These consist, as in other regions, of distended blood tracks, whose walls are formed by a single layer of endothelium. In the tube they are found more especially towards the peritoneal aspect. They exhibit great differences in size, varying from channels, whose walls on section are formed of three or four cells, to large, greatly expanded blood lakes. As they correspond in structure to the blood sinuses which develop in the muscular coat of the uterus during pregnancy it was thought that a study of their mode of formation might cast some light on the process at work in the case of the uterus.

In shape they exhibit wide variations; some are more or less circular or oval, whilst others are drawn out and may extend for a considerable distance through the tubal wall. These differences may, to some extent, depend on the plane in which they are cut across in the sections. In most cases they/

they do not, however, possess such a regular contour. Their boundary is usually irregular in shape, sometimes to a remarkable degree. From the main channel arms or branches of varying size are projected into the wall of the tube. In many cases the tracks are tortuous. The appearances exhibited suggest strongly that the sinus-like space once formed continually increases in size at the expense of the adjacent tube wall. In the extension of their boundaries they are often seen to pursue the line of least resistance. They are, for example, often seen to skirt bundles of muscle which are interposed in the path of their advance. In many cases the off-shoots are seen to burrow along between two such muscle bundles. In fact the appearances revealed indicate that the surface irregularities are dependent almost entirely on such mechanical influences. It will be noted that in the unevenness of their boundary surfaces these sinuses coincide with the appearances presented by the similar spaces in the uterine muscular coat (Figures 78-84).

It would seem that the large blood spaces must be formed from pre-existing vessels and the structure of their wall would seem to warrant the conclusion that they are developed for the most part, from capillary vessels. There are no structures in the/

the normal tubal wall in the least corresponding to them in dimension. Their origin is also indicated by the fact that it is sometimes possible to determine the existence of a fine capillary connection between two adjacent spaces, which then simply look like two enormously distended regions of the same blood track. It will be pointed out, however, that even thick-walled vessels may assume like invasive properties, when deprived of their investing and supporting muscular coat.

How are they formed? The fact that with an increase in size there is a corresponding increase in the number of the cells forming their wall indicates that they are not formed by a process of mere mechanical expansion. The fact, moreover, that, although there must be a rapid increase in the circumference of the wall, there is in none of my specimens any evidence of a division of the component cells, would suggest that there is something more than an increase in the pre-existing lining cells. I would advance the following observations in support of the fact that in the process of expansion the walls are continuing coming into line with, and embracing the adjacent connective tissue cells of the tubal wall. The process is demonstrated with great precision in one, the youngest of my tubal pregnancies; in it the tissue destruction, /

destruction, which in the other specimens, has obscured the exact nature of the changes present, is not so marked. For this reason the following statement of the finer histological changes refers, unless otherwise noted, to the youngest specimen of the series

In all my specimens the formation of the sinuses has occurred in the tubal wall to a very marked degree.

It has already been mentioned that in many of the sections there is seen a process of fluid imbibition by the connective tissue cells. This is associated with the formation of vacuoles, often of large size and sometimes several in number, within the cell body, the protoplasm of which is displaced to the periphery. The many and varied appearances exhibited in the process of the fluid distension of the cells have been described on a former page. It was also observed that where two such cells lay close together there was often noted an amalgamation of the fluid space permitted by a disappearance of the intervening cell protoplasm. Where this occurred in the case of two or more cells lying end to end there was produced an elongated fluid track, which, in many instances could be traced through three or more cells in the same section. (Plate XI) Where the cells lie side by side the disappearance of the separating films of cell substance results in the formation/

formation of a more or less circular space filled with clear fluid bounded by two cells. The various stages in this process are easily traced. By amalgamating with an adjacent, similarly distended cell we have the production of a space formed by three cells and so the process would seem to be capable of extending till a large space may be created.

It has already been noted, also, that these changes in the connective-tissue cells, which would seem to be dependent on alterations in their osmotic tension are exhibited in a manner exactly similar by the endothelial cells of the blood vessels, in fact that the process in each case is in the beginning determined by one common factor, namely the tissue changes caused by the presence of the growing ovum. Where a vacuolated endothelial cell abuts on a similarly affected connective tissue cell which is placed more or less parallel to it, there is again apt to be an amalgamation of two spaces.

This appearance is often easily recognised in different parts of the circumference of such a sinus-like space. On plate XI is shown such an expanding vessel - on the left lower aspect of this there is seen a connective tissue cell coming/

coming into communication with the invading blood space. The disappearance of the fine film of the lining cell, which separated the space produced by the union of the two vacuolated cells, results in the extension of the blood cavity up to the level of (Figures 86,87) the outermost cell. It can easily be understood that this process will lead to the steady expansion of the space. It can also readily be seen that any obstacle in the shape of a muscle bundle, will effectually bar at that part the progress of the extension process and explains the rationale of the manner in which the expanding space skirts the muscle and sends an off-shoot between the two interposing bundles. Outward projections of the blood cavity thus produced often look like new blood vessels, but their real nature is easily determined by tracing them by serial sections when they are found to consist of cul-de-sacs. Although, for the most part, the formation of such sinuses would seem to occur at the expense chiefly of the finer vessels it is interesting to note that the same process may be detected in the thicker-walled vessels. On figure 85 is shown such a vessel in which there has been a detachment of the investing muscular coat. The lining layer thus released is seen to be throwing out projections into the tubal wall/

wall in the manner described above. These look at first sight like parts of complete blood channels. On tracing by serial tracing they are found, however, to terminate blindly. It is interesting to note that in the vessel figured, as in many others, the projection into the surrounding tissues of the finger-like processes is occurring almost entirely in the direction of the growing foetal cells. This is natural in view of the fact that the change is dependent on the foetal influence. It is obvious that such an expansion of the vessel walls in the case of those vessels close to the embryonic structures, culminates in a wholesale transference of the necessary nourishment towards the intervillous space. It will be subsequently pointed out that a process entirely analagous in every respect may occur in the uterine mucosa in the case of an ordinary pregnancy.

MODE/

MODE OF FORMATION OF NEW BLOOD VESSELS

IN WALL OF PREGNANT TUBE.

In places throughout the wall of the tube in cases of pregnancy there is evident a new formation of blood vessels. As in the case of the newly formed blood sinuses described in the last paragraph this process is most evident towards the peritoneal aspect of the tube, and, as a matter of fact, the two processes are often found occurring hand in hand. The formation of the new vessels is best studied round the circumference of the blood lakes. Here there is often detected a rich budding out of the wall in the form of fine capillary off-shoots (figure 79 - 82 and plate X) Even in the case of a small sinus there may be found six, eight or more such capillary off-shoots being projected into the surrounding tubal wall. In some cases these are found on tracing by serial sections to end blindly after running for a short distance in the tubal wall, in other cases they appear to extend through the tubal wall for a considerable interval and they can be noted in many instances entering into an anastomotic communication with one another.

Whilst the process is noted in all my specimens where the tissue destruction is not excessive/

excessive, it is clearly traced in only one of my pregnant tubes, and the following account of the changes is in the main, derived from the study of this tube. Whilst, at first sight, the mode in which new vascular formation takes place in the pregnant tube may seem to be irrelevant to the subject under discussion its importance will be recognised when we come to the discussion of the changes produced in the uterine mucosa by the presence of the growing ovum. Round the periphery of the early developing embryo a formation of new capillary vessels has been noted in the young decidual membrane, and the investigations here recorded would seem to cast considerable light on the factors probably in operation in the case of the uterus. Whilst, as in the uterus, the change is in some parts recognisable in the immediate proximity of the ovum the exact histological features of the process are obscured in this region of the tube by the excessive degeneration of the tissues.

I have already referred to the fact that, in the fluid spaces in the substance of the connective tissue cells, it is often possible to recognise the presence of well-preserved red blood corpuscles (Figure 76) This fact would seem to provide a clue to the manner in which the new capillary off-shoots are/

are formed. In the description of the vacuolated condition often exhibited by the connective tissue elements it was mentioned that where two or three such cells lie end to end there is apt to be a running together of the fluid spaces with the creation of a track continued along for a corresponding distance (Plate XI .) In last paragraph, also, it was noted that where such a cell lay apposed to a vacuolated endothelial cell there was noted in many cases an amalgamation of the two cells and a subsequent extension of the blood cavity to a corresponding degree. The new vessel formation would seem to be dependent on the same cause. Where a connective tissue cell is set at an angle to a vacuolated endothelial cell there is seen a fusion of the fluid spaces, and, with a disappearance of the film of cell substance intervening between this new fluid track and the vessel lumen, there is produced a new capillary vessel. On figure 89 is shown a vessel exhibiting these changes. At one part there is seen a vacuolated endothelial cell. At another part a capillary off-shoot in the earliest stage of its formation is seen. The endothelial cell has established a communication with the adjacent connective tissue cell, and this, again has fused with another connective tissue cell. As the result of the/
the/

the disappearance of the fine pellicle of the cell substance of the endothelial cell corresponding to that shown in the case of the cell seen in the lower part of the figure there has been formed a complete and un-interrupted channel extending through the length of three cells. It will be noted that in the process the nuclei of the endothelial cells are drawn into line with the direction of the escaping fluid.

Similar appearances are shown in Plates X & XI and throughout the tubal wall the vacuolated connective tissue cells are seen. In the neighbourhood of the vessels these have served in the formation of the new capillary twigs. In Figure 70 - 71 is demonstrated a fact of considerable importance, namely that an apparent projection of a solid bud from the endothelial layer is seen, on tracing in serial section, to consist, in reality, of a complete canal, the wall of which has merely been cut across at a tangent.

How is the disappearance of the cellular film, which is essential to the process, to be explained? It seems not improbable that this may be due to a mechanical yielding to the intracellular tension produced by the distending fluid. It may, on the other hand, be due to the dissolving process which/

which is occurring, for it is often possible to detect a nucleus devoid of cell substance lying in a fluid space. The cytoplasm has apparently disappeared in solution.

It will, then, be seen that the two processes described in the last two sections of this research, the formation of the sinus-like expansions of the vessels and the formation of new capillary twigs from the pre-existing vessel walls, are to be traced to one and the same factor, namely an alteration in the cell protoplasm determining an absorption of fluid from the vessel lumen or the tissue spaces. This, we have seen, is, in all probability, to be explained by a change in the constitution of the cytoplasm which is associated with the liberation of crystalloidal molecules and an increase in the osmotic pressure of the cell.

We have arrived then at a conclusion which to me seems to be of the greatest importance, namely that the three changes exhibited by the vessels in the tubal walls are traceable to the same common factor. We have already adduced evidence which proves beyond dispute that the dropsical infiltration and teasing asunder of the structural elements of the vessel walls, which is found to a marked degree in the pregnant tube and which is more and more evident, the/

the nearer the engrafted ovum is approached, must be dependent on tissue changes which result in an active imbibition of fluid from the vessel lumen. This was manifested in the earliest stages of the process by a vacuolation of the endothelial cells or an oedematous accumulation on the inner aspect of the vessel wall. As the condition progressed the degenerationⁱⁿ tissues of the vessel wall and the connective tissue cells entangled in these were seen to exhibit the same changes, until ultimately there is produced, especially in the immediate proximity of the ovum a wholesale detachment and spreading apart of the vascular wall with a liberation of the contained blood. We have now advanced evidence which seems to indicate that in the expansion of the vessel walls and in the throwing out of the capillary twigs, exactly the same process is in action, the only reservation being that in the two latter conditions the endothelial and connective tissue cells alone share in the changes.

If our interpretation of the phenomena be correct we have derived from our investigations information which tends to establish the close structural relationship between endothelial and connective tissue cells; this is found in the fact that the latter are able under certain circumstances, not/

not only to range themselves alongside and to take part in the formation of the endothelial layer of the expanding vessel, but they can, also, become canalised to form the lumen of a capillary vessel.

In this place it must be mentioned that the intra-cellular formation of capillary vessels has been repeatedly described by other investigators. All I claim for the observations here recorded is that besides adding a small contribution to the evidences in support of this conception, they would indicate that the rationale of the process is to be found in protoplasmic changes induced by some external influence which in the case under discussion, is, in all probability to be identified with the biochemical influence emanating from the chorionic cells.

S U M M A R Y.

1. In the pregnant tube there occurs an extensive formation of blood-sinuses and of new blood-vessels. These changes are especially evident in the fine-walled vessels. They are often present, however, in those with thick walls.

They may be seen in the immediate proximity of the ovum, where they both assist in carrying the maternal blood towards the foetal cells.

2. Both vascular alterations are due to an active fluid imbibition by the endothelial and the connective tissue cells. The expanding force is not a heightened intravascular pressure. The new capillary channels are formed in response to exactly the same tissue changes as lead to the irregular oedema and haemorrhage. In this case, however, the blood fluid and cells are being drawn along definite intracellular tracks. The connective tissue elements are able to form the new endothelium.

SECTION IV.

MATERIAL. For this investigation I have been able to procure only one specimen. It consists of an entire uterus removed by vaginal hysterectomy, in the anterior wall of which near the fundus a small fragment of what at first looks like ordinary placental tissue is embedded.

SECTION IV.

MODE OF ACTION OF CHORIONIC STRUCTURES ON MATERNAL TISSUES -

PLACENTAL REMAINS.

The specimen is a small, dark, irregularly shaped mass, 1/2 in. wide by about 1/4 in. in length. The mucous membrane of the rest of the uterus is deeply congested. All the history of this specimen that I can give is that it was obtained from a woman who had aborted five months previously.

I propose to describe the microscopic appearances presented by this specimen under two headings: (1) The Placental Remains and (2) The

ACTION OF THE CHORIONIC CELLS ON THE
MATERNAL TISSUES AS SEEN IN RETENTION OF
PLACENTAL FRAGMENTS.

MATERIAL. For this investigation I have been able to procure only one specimen. It consists of an entire uterus removed by vaginal hysterectomy, to the anterior wall of which near the fundus a small fragment of what at first looks like ordinary blood clot is adherent. On section the clot is seen to be sharply cut off from the adjacent paler muscular tissue of the uterine wall. This projects as a distinct polypoidal swelling into the uterine cavity at the point of the attachment of the clot, and in it a number of dark-red patches are seen: these, as will be shown subsequently, correspond to greatly distended blood spaces. The clot measures $\frac{1}{2}$ in. wide by about $\frac{3}{4}$ in. in length. The mucous membrane of the rest of the uterus is deeply congested. All the history of this specimen that I can give is that it was obtained from a woman who had aborted five months previously.

I propose to describe the microscopic appearances presented by this specimen under two headings: (1) The Foetal Remains and the Changes in /

in the Muscular Wall adjacent to these, (2) The Changes in the Mucous Membrane at a distance from the Placental Villi.

(1) THE FOETAL REMAINS AND THE ADJACENT
MUSCULAR TISSUE.

The placental remnants consist of a number of villi imbedded in the blood clot. The ectodermic and the mesenchyme cells are, in some places, well-preserved and, in other places, markedly degenerated. For the most part the villi do not come into direct contact with the uterine tissue. Here and there, however, they lie up against this and in one or two places they may actually be seen situated in a vessel. The general appearances are seen on Plate XIII.

The Maternal Tissues. In the proximity of the villi the mucous membrane has almost entirely disappeared. Here and there a gland or two surrounded by the stroma cells may be seen. These are usually enlarged in a decidual manner. These regions correspond to the incursions of the mucosa into the muscular tissue. The muscular tissue immediately bordering on the blood clot is in a state of coagulation /

coagulation necrosis, exactly as described in the wall of the pregnant tube. As in the latter site it is richly sprinkled with red blood cells. Immediately subjacent to this the tissues are infiltrated with leucocytes chiefly of the polymorphonuclear type. Even at a distance from the villi the muscular tissue is degenerating. In these respects the changes coincide with what I have already described in connection with the pregnant tube. Decidual and other alterations in the connective tissue elements will be noted in a subsequent section.

The Changes in the Vessels correspond to those observed in the pregnant tube. As I have discussed these in full in the last section, and as I intend to go into the subject again in connection with the maternal tissue changes in chorionepithelioma, it will be necessary to refer to them here only in brief. In all the sections there is a haemorrhagic escape from a large number of the vessels, even at a distance from the region of the villi. In the marginal area the blood is passing directly into what corresponds to the intervillous space through the gaping mouths of the opened-up vessels, or it is seen traversing the maternal tissue intervening between the vessels in the neighbourhood of the foetal /

foetal remains and the main blood space. The fact that these changes are widespread, whereas at no spot is there visible any direct invasion of the uterine wall by the chorionic cells, proves beyond doubt that the blood escape is not due to a foetal infiltration and destruction of the vessel walls. As before the alterations in the vessel walls demonstrate convincingly that the process is due to tissue changes, that determine an active imbibition of the blood fluid and later of the blood corpuscles. The stages in the process are just as easy to follow as in the pregnant tube. (Figures 108, 109, 110, 111, 112). In Figures 113 - 114 is shown a vessel near the intervillous space along the interior of which a villus has grown. It is now markedly degenerated and there are no foetal cells attached to the wall. This section demonstrates the untenability of the conception that the blood does not leave the vessel lumen till the wall is completely destroyed. Here the red cells are seen streaming in quantity through the wall, away from the foetal elements, in response to the tissue changes which these induce. This exodus of the red cells into the surrounding tissues is present both from the vessels coursing through the necrosed regions and from those whose walls are well-preserved. On the whole it is more evident in the former, and this doubtless because of the greater intensity of the tissue changes.

As/

As in the pregnant tube it is found that a decidual formation in the tissue cells prevents the irregular blood escape. On Figure 115 is seen such a vessel in the close proximity of the foetal elements. The enlarged cells correspond to the cells of the stroma of the mucous membrane where this has dipped into the superficial muscular layers. Lying amongst the decidual cells a number of leucocytes are seen.

In many places, especially in the proximity of the villi, there is a marked distension of the vessels. In some instances this has resulted in the formation of sinus-like expansions such as I have described in the wall of the pregnant tube. In these cases the wall is formed by a layer of flattened cells only. As before there is often an irregularity and unevenness of the bounding walls. In other cases the increase in diameter has involved the vessels coursing through the degenerating tissue in the neighbourhood of the villus remains. The confines may be regular but they are often ragged and uneven, and it looks as if the expansion were due to a gradual solution of the necrosed tissue by the blood fluid. Round the periphery of these spaces the red corpuscles are usually seen streaming into the adjacent tissues through the wall, in a manner similar to/

to that present in the wall of the pregnant tube. (Plate XIII). As already mentioned where these blood tracks approach the intervillous space the red cells which escape through their walls are often seen passing across the maternal tissue partition intervening between the two blood regions.

(2) CHANGES IN THE UTERINE MUCOUS MEMBRANE
AT A DISTANCE FROM THE FOETAL
REMAINS.

Round the uterine cavity the mucous membrane is well retained. To the naked eye it is seen to be deeply congested. In this section I wish to refer to important microscopic changes which it exhibits. For purposes of description I have chosen a region of the mucosa at the pole of the uterine wall opposite to that to which the blood clot is adherent. In the sections no foetal cells are present and the changes are therefore not dependent on a direct invasion by the chorionic elements.

In many places there has been a loss of the superficial epithelium, and in some places the surface layers of the stroma with the gland orifices are/

are wanting . Apart from this the glands are normal in appearance; (Figure 116.). In the vessels and the interglandular connective tissue there are changes of the most profound importance from the point of view of one of the objects of this research. In most places there is present a well-marked hæmorrhagic escape. This has involved the upper two thirds of the mucosa; the lower third has almost invariably escaped. The bleeding has led to a ploughing up of the stroma, the cellular elements of which are often widely separated from one another. For the most part the extravasation is greatest in the surface regions. The mode of the blood escape from the vessels is often easy to trace. In the better supported vessels the stroma cells are becoming stripped-off, often in concentric layers from without inwards. When this has occurred to the extent of leaving only the intimal cells, or even before, the red cells are liberated and are seen to be streaming in quantity through the wall into the surrounding tissues. There is often present a wholesale opening-out and displacement of intima as well as surrounding stroma by the escaping blood. This results in an expansion of the vessel and then it is usually impossible to distinguish original intimal from original supporting cell. (Figures 117 - 123).

We thus see that in many respects the changes exhibited by the mucous membrane in this specimen coincide with the changes which I have described in connection with menstruation. The vascular and surrounding stroma alterations are identical in nature with those previously recorded. The only difference is one of degree - in this case the bleeding is greater than is found in normal menstruation. This factor probably accounts for the separation of the surface epithelium and stroma which has occurred in places, though, of course, it is possible that this is an artefact.

How are we to account for these remarkable changes, which, so far as I know, have never before been noted in this condition? The hæmorrhage present is clearly not due to an opening-up of the maternal vessels by a direct invasion of the chorionic cells. On the other hand it would seem likely that they must be dependent on the presence of the foetal elements. It seems to me that the hæmorrhagic escape must be determined by the same factor which, in the muscular wall of the uterus underlying the villous fragments in this specimen, and in the wall of the pregnant tube, results in an irregular and sometimes excessive bleeding from the vessels, even at a long distance from/

from the actual locality of the foetal cells. We have seen that in the wall of the pregnant tube the condition is probably due to the liberation of some substance of a chemical nature which, while acting most vigorously in the immediate proximity of the foetal cells, gradually extends the sphere of its activity to a remote distance. The excessive extravasation exhibited by the mucosa in this specimen is, in all probability, due to the well-demonstrated susceptibility of the stroma tissue and vessels. This I have referred to in detail in a preceding section and I have there shown that the structural peculiarities of the stroma protoplasm enable it to respond with the greatest advantage to the influence which determines the menstrual changes. The chorionic substance in this instance probably reaches the mucosa directly. It is clear that the surface of the mucosa will be continually bathed by any material in solution escaping from the villi. This explanation of the phenomena seems to me the more rational one, though of course it is impossible to say with certainty that the chorionic influence is not transmitted to the mucous membrane through the medium of the blood stream.

A fact of considerable clinical importance is/

is revealed by the study of this specimen. The severe bleeding from which the patient had suffered was derived not only from the vessels in the immediate proximity of the villous remains, but also from the mucous membrane at a considerable distance. The appearances warrant the conclusion that a large amount of the blood escape was derived from this source. The conditions present here correspond in many details to those seen in the pregnant tube, where there is apt to be a free blood escape from the vessels at a remote distance from the chorionic cells. This is especially true of the finer vessels. In several of my specimens there had obviously been a continual oozing from the small vessels towards the peritoneal aspect of the tube.

S U M M A R Y.

- (1) In the case of retained placental fragments the vascular changes coincide with those seen in the pregnant tube. The vessel walls open up in response to the tissue changes induced by the substance derived from the chorionic cells. The oedematous and blood escape are often present at a long distance from the villi.

(2)/

- (2) In the mucous membrane at a distance from the villi there are present stroma and vascular changes similar to those normally found during menstruation.
- (3) The bleeding from which the patient suffered was derived in part (and probably largely) from the mucosa at a distance from the villous remains.

THE MODE OF ACTION OF THE CHORIONIC EPITHELIUM
 IN THE MATERNAL TISSUES OF STOMACH
 (IN CHORION-EPITHELIOMA).

MATERIAL. SECTION V.

MODE of ACTION of the CHORIONIC EPITHELIUM
 on the MATERNAL TISSUES -

CHORION-EPITHELIOMA.

The fourth case, which included
 sections from the lungs in which there had
 occurred metastatic deposits, was obtained
 post-mortem. In all the cases the preser-
 vation, as judged by the condition of the fetal
 elements, is excellent.

The investigations recorded in
 the following paper were carried out with the idea
 that

THE MODE OF ACTION OF THE CHORIONIC EPITHELIUM ON THE MATERNAL TISSUES AS STUDIED IN CHORION-EPITHELOIDOMA.

MATERIAL.

This consists of four uteri, which were the seat of a well-marked chorion epitheliomatous infiltration. Three of the specimens were removed by vaginal hysterectomy and were immediately transferred to the hardening fluid.

The fourth case, which includes sections from the lungs in which there had occurred Metastatic deposits, was obtained post-mortem. In all the cases the preservation, as judged by the condition of the foetal elements, is excellent.

The investigations recorded in the following pages were carried out with the idea that /

that a study of the changes induced in the uterine wall by the malignant invasion of the cells of the foetal ectoderm might shed still further light on the manner in which the embryonic structures, under normal circumstances, establish their intimate relationship with the maternal tissues in the case of a uterine pregnancy.

In the last two sections we have acquired evidence which tends to prove that the orthodox conception of the exact manner in which the foetus is furnished with its supply of maternal blood must be completely modified, at any rate, in the case of a tubal pregnancy and in the case of retained fragments of placenta where the chorionic cells have preserved their activity. In both of these conditions, which, though pathological, correspond to a foetal invasion of the maternal tissues of a benign nature, we have seen that in response to the presence of the embryonic elements there are set into /

into action complex changes in the maternal tissues which result in their actively imbibing the blood fluid and cells and, in the case of the vessels in the immediate proximity of the foetal ectoderm, culminate in a wholesale escape of the red blood corpuscles across the space intervening between the vessel lumen and the villous line of advance. We have seen that the maternal vessels are opened up by a process of this nature and not by a direct invasion and replacement of the tissues of the vessel wall by the advancing chorionic cells, though in many cases the appearances would, at first sight, seem to warrant such a conclusion.

In the case of chorion-epithelioma we are dealing with a tumour growth composed of masses of foetal cells, which actively invade the wall of the uterus. After a large amount of discussion (it is doubtful whether any tumour has ever given rise to so much dispute as to its origin) this growth has now been definitely proved to owe its origin to a malignant over-growth of the epithelial elements of the chorionic membrane. Hence the name. The indisputable demonstration of its true nature we owe, in the main, to the researches of Marchand on the con-⁽¹⁷⁾ tinent, and to Teacher in this country.⁽¹⁸⁾

Prima/

Prima facie it would seem likely that the manner in which this tumour is provided with its supply of maternal blood would correspond to the manner in which the ovum engrafted in the uterine mucosa opens up the maternal vessels, for this is accomplished, as we know, by the activity of its epithelial covering. In either case - in the benign activity of the cells of the embryo which has burrowed into the uterine mucosa, and in the malignant action of the cells of the neoplasm - the object of the tissue changes induced is the acquisition of a plentiful supply of mother's blood. In either case we are dealing with structures which are, in the main, to be considered as parasites deriving their sustenance from the maternal blood.

Chorion-epithelioma, then, may be defined as an over-growth of the cells of the foetal ectoderm, which, for some reason or other, which we still imperfectly understand, has during or after a pregnancy assumed a malignant tendency. This is manifested by an infiltration and destruction of the tissues of the uterine wall, sometimes to the extent of burrowing right through to the peritoneal surface. As is well/

well known this hyperplasia of the chorionic cells is very apt to ensue subsequent to the development of a Hydatidiform Degeneration of the foetal villi. On section the uterine wall is seen to be studded with clumps of the foetal cells, which often appear to be cut off from one another and lie as islets embedded in the uterine wall. It is usually easy to recognise in these masses both of the cellular elements of the foetal chorion - the rounded or polygonal cells with large nuclei, corresponding to the Langhans' cells of the ectoderm and the plasmodial multi-nucleated masses, which correspond to the syncytial covering of the foetal surface. The main changes in the maternal structures are seen in the production of a wide spread oedema and blood extravasation, the latter being especially marked round the masses of the foetal cells. In addition there is induced a progressive degeneration of the muscle of the uterus. The fibres swell up, the nuclei become large and pale. This is followed by a disappearance of the outlines of the fibres, which often coalesce to form a homogeneous structureless mass devoid of nuclei. In later stages of the degeneration the muscle elements disappear altogether, apparently entering into a state of solution.

This/

This investigation is concerned more especially with the histological changes exhibited by the maternal tissues, and more particularly with regard to the alterations in the walls of the maternal vessels.

As already mentioned one of the most characteristic features of this tumour growth is the excessive haemorrhage which its presence provokes. In the literature the mechanism of this is supposed to depend on an infiltration or corrosion of the vascular walls by the chorionic cells, which give way, releasing the contained blood which is extravasated by the force of the blood stream, and thus furnishes the nutriment of the growing cells of the tumour.

The orthodox conception of the process is thus expressed by Teacher in his admirable monograph:-

"The advancing tumour attacks the vessel from without, destroying and replacing the wall When it reaches the endothelium the tumour cells tend to spread along just under it for some distance, so that the vessel may come to have the appearance of a tube of endothelium in a sheath of large tumour cells Sometimes a plug of tumour regularly invaginates the endothelium into the lumen. The invaded/

invaded blood vessels (at least those attacked from within) dilate; this peculiarity is particularly striking in the vaginal metastases which are usually taken to be varicose veins." The haemorrhage is caused by the fact that "finally the endothelium disappears or gives way. When this occurs, on the one hand the tumour cells enter the vessels and on the other extravasations of blood into the tumour take place". According to this description of the changes, which so far as I can discover, embodies the conception universally accepted, we note that for an escape of the contained blood there must be a local destruction of the vessel wall by the infiltrating tumour cells. This once accomplished, we have a mechanical exodus of the liberated blood.

Teacher in another paragraph states that "the tumour grows into the mouths of the uterine sinuses, attaches itself and invades them from within". According to this description of the process, then, the foetal cells are bathed in the maternal blood by one of two different methods; (1) they destroy the vessel wall and in this way create a gap through which the blood is poured out, or (2) they grow into and along the vessel lumen in a manner which, in some cases, /

cases, is similar to that in which the villi extend along the veins of the tube wall, in the case of tubal pregnancy, and along the uterine veins in the case of normal pregnancy. It will be seen that these conceptions regarding the mode of action of the tumour cells in the condition we are studying coincide accurately with the almost universally accepted view of the method of action of the chorionic cells in the case of a tubal pregnancy, and, as will be noted later, also in the case of normal uterine pregnancy. It was for the purpose of testing the validity of these ideas that I have carried out the investigations here recorded.

In all my specimens the blood extravasations, though most evident in the immediate proximity of the foetal cells, are not confined to this region. Scattered irregularly throughout the maternal tissues there are numerous areas of blood escape round the vessels, and this even at a considerable distance from the site of the cellular invasion. It is also distinctly present in the lung tissues in which there has been the occurrence of metastatic deposits derived from the primary source. In all of the specimens it was possible without the least doubt to recognise the red cells leaking from vessels in whose/

whose neighbourhood there were present no cells in the least resembling those of the chorionic membrane. These observations indicate that there must be in operation some influence determining the blood escape through the vessel walls other than the direct locally infiltrative and destructive effect of the chorionic cells. The more distant haemorrhages, it is clear, must be provoked in some way or other by the presence of the chorionic cells. The fact that the blood exit through the vascular walls becomes, on the whole, more and more marked the nearer the tumour masses are reached would indicate that this chorionic influence, whilst naturally exercising its most potent action on the nearest maternal structures, spreads directly through the tissues, becoming less and less powerful until ultimately it is insignificant or becomes lost altogether. The probable nature of this influence I shall discuss in a special paragraph in the later part of this research. In the meantime I shall be content to refer to it exclusively from the aspect of the structural changes which it induces in the maternal tissues.

In Plate XIV. is shown a fine vessel through the wall of which there is seen a passage of the red cells/

cells into the neighbouring tissues. The boundaries of the vessel are unimpaired round its entire circumference; in other words, there is no trace of the destructive process such as is demanded by the orthodox conception cited above. At a small distance there are seen the chorionic cells, but between these and the vessel wall there is a distinct interval devoid of the foetal elements. A similar streaming of the red corpuscles through a vessel at a distance from the foetal invasion is seen in Plate XVI.. The fact that one can detect with ease the passage of the individual cells through the vessel wall, disproves with certainty what otherwise might have been urged, namely that the haemorrhage in these cases is derived from the same or another vessel whose wall had been invaded in an adjoining part of the uterine wall. I maintain that these appearances which are found with ease in all my sections, demonstrate beyond cavil that there is in existence some process different from that advanced by previous investigators on the subject. We see also that by this influence the foetal elements are brought into contact with the maternal blood. It will be noted that, so far, these investigations coincide/

coincide with those which I recorded in connection with the blood escape in the pregnant tube and in the condition where placental fragments are retained in utero.

As the result of these observations we are compelled to amplify the conception entertained by Teacher and others. If both views be correct, then we have to deal, in regard to the manner in which the tumour masses acquire their nutriment in the shape of the maternal blood, with two separate and distinct processes. We have, in the first place, a local destruction of the vessel walls by the direct chorionic infiltration with a subsequent mechanical outpouring of the blood over the foetal masses, and we have, in the second place, some tissue or vascular alterations, which are independent of an actual chorionic invasion. I shall advance evidence in a later part of this investigation which tends to indicate that the important factor is not the local breach or breaches created in the vessel walls, but that this process is probably to be looked upon rather as an incident in the advance of the tumour cells than as the cause of the blood escape.

In the meantime, I shall pass on to consider the possible factors responsible for the escape of/

of the red cells from the vessel lumen where a direct invasion by the foetal cells can easily be put out of court.

CAUSE OF THE BLOOD ESCAPE FROM THE MATERNAL VESSELS.

In pursuing this enquiry I propose to adopt almost exactly the same line of procedure as was found valuable in the case of the pregnant tube. It will be useful again to consider in the first place the changes exhibited by the thicker walled vessels, where the process at work is, for a reason noted in the previous investigation, more clearly deciphered, and, in the next place, to review the alterations in the fine-walled vessels.

In none of my sections are the structural changes in the vessels of the uterine wall so marked and so wide-spread as was found in the tubal wall in the case of a pregnancy in that site. The actual process in operation is, however, none the less easy to distinguish.

Here again the process may be divided into two more or less distinct stages. In the first place we have a dropsical opening-out of the tissues. This/

This is followed by the haemorrhagic escape from the vessels. We have already noted that an oedematous infiltration of the uterine wall is one of the most characteristic changes induced by the presence of the chorion-epitheliomatous masses. It is wide-spread and reaches its maximum in the immediate proximity of the chorionic cells. By its means there is produced a spreading apart of the muscle bundles and a teasing asunder of the individual muscle fibres. The process is most evident, for the most part, in the environment of the vessels, and can be seen leading to an opening out of the structures forming the vessel walls. In many places it is easy to detect oedematous tracks ploughing their way through the vessel walls into the neighbouring region where they usually expand into wider spaces, because of the easier separation of the tissue elements. Sometimes in the better supported vessels this condition is limited to the vessel wall but as soon as it involves its entire thickness, and frequently before, the neighbouring tissues are involved in the process. Along the tracks thus created it is, in many places, possible to discover the escape of the red cells. In fact the dropsical infiltration is such a constant/

constant precursor of the corpuscular escape that, as in the case of the pregnant tube, it must be looked upon as a preparation for the exodus of the more solid elements of the blood. Any light thrown on the process underlying this watery exudate must furnish us with important evidence in our search after the secrets underlying the mechanism by which the vessels open up and pour their blood into the surrounding tissues and which in the neighbourhood of the tumour masses determines at once the way in which the foetal elements are furnished with their necessary nourishment and the manner in which there is produced the haemorrhage which is so typical a symptom of this disease, and which is often so severe as to endanger the life of the patient.

CHANGES IN THE VESSELS.

If we examine the vessels in the uterine wall we observe in many places and even at a considerable distance from the chorionic cells the appearances represented on figures 124 - 129. In the vessels represented there is seen a swelling and bulging towards the vessel lumen of the endothelial layer of cells. Sometimes this is indicated by a/

a fluid distension involving the individual cells (figures 124-6) in other cases it is represented by a dropsical accumulation in the immediately sub-endothelial space, which has resulted in a wholesale floating up of a sheet formed by several of the cells (figure 128). The fluid expansion of the isolated cells, which project into the lumen like a row of beads set into the vessel wall, is a constant precursor of the more marked accumulation. As the result of the intra-cellular collection there is produced a clear space enclosed by the fine pellicle of cell substance with the nucleus displaced outward to the periphery and for the most part in relation to that pole which is directed towards the centre of the lumen. Here we have again the "signet ring appearance," a condition we have noted in several other sections of this research. It is obvious that these appearances can be due to one cause, and one cause only, namely some alteration in the cell protoplasm, which has determined an absorption or imbibition of fluid from the vessel lumen. When the cellular distension reaches a certain degree there occurs a separation of the confining layer of cell substance. Whether/

Whether or not this is dependent, as is usually described in connection with similar cell changes elsewhere, entirely on mechanical causes, I am unable to state with certainty. It seems to me, however, not unlikely that the cytoplasmic changes, which have culminated in the opening up of the cell substance by the fluid imbibed, may of themselves determine the softening and ultimate giving way or solution of the remaining portion of the cell substance, which has been displaced to the periphery. I employ the word solution here advisedly because it has been repeatedly borne in on my mind in the course of my researches that there must be, in association with the protoplasmic changes with which we are at present concerned, some gross alteration in structure which not only determines an attraction for fluid, but which also permits of the changed cytoplasm, which in some instances may be the whole substance, becoming dissolved in the entering fluid. This would seem only natural and yet so far as I can gather it has as yet not found the place its importance merits in the calculations of pathologists. What the exact nature of the changes in operation is, we are still unable to state with precision, but it seems to be certain that the fluid absorption by the cell, and which/

which leads to a collection in the cell under a hydrostatic pressure greater than that in the vessel -lumen must depend on a chemical alteration in the cell substance associated with a liberation of crystalloidal elements. This creates an enhanced intracellular osmotic tension and determines a diffusion from the blood vessel lumen (or the tissue spaces, in other cases) into the cell. The crystalloids thus produced or rather, in all probability, liberated, will enter into solution, and it is easily seen that by this means there must occur a certain diminution in the total solid of the cell contents. It seems to me not improbable that exactly the same process as that responsible for a softening and opening up of the cell body may in its progress ultimately involve the cell pellicle and thus, by a means which is not simply mechanical in nature, throw the intracellular cavity into direct communication with the surrounding space. This conception, in addition, is in conformity with the more recent researches into the structure of the cell, which tend to prove that in most animal cells there is no definite and differentiated cell-membrane corresponding to the envelope/

membrane) from the blood vessel lumen, which is a region of lower, to the tissue space, which is a region of higher osmotic tension. We thus see that the same process, which led to a fluid distension inside the cells, has resulted in a dropsical accumulation outside the cells. It can only be explained as due to the presence in the tissue space of crystalloidal elements, which have been set free in consequence of the activity of the chorionic cells. There can be little doubt that these crystalloids are again derived from the changes produced in the protoplasm of the cells constituting the vessel wall. The changes leading to this dropsical infiltration of the inner portion of the vessel wall, by opening out the tissues, may permit of an escape into the corresponding area, of the corpuscular elements of the blood (Plate XVI.).

So far, then, we have no difficulty in understanding how the innermost portion of the vessel walls become opened out, and how to this extent, there may be a liberation of the blood contained in the vessels. How is the teasing asunder of the tissue elements, and, in the case of vessels other than the very finest, of the outer portion of the wall/

wall, to be explained? We have seen that, if we satisfactorily explain these phenomena, we have little difficulty in determining the rationale of the escape of the red blood corpuscles into the surrounding tissues. From the fact that their structure results in a forcing into prominence of the successive steps of the process, I shall still confine my remarks to the thicker-walled blood vessels. The next stage is seen in an opening of the vessel boundary in the region immediately external to that already referred to. Here again it is easy to determine that there must still be operation the same osmotic influences. These fluid tracks are represented often by a sort of honey-combing of the muscular tissue of the vascular wall (Figure 128) ; in this, the earliest stage of the process, there are still present bridging and interlacing processes of the degenerating protoplasm which interrupt the completeness of the tracks. In some cases on section this appearance is evidenced by the presence in the wall of a large number of spaces, varying from a size just recognisable with the highest powers of the microscope to comparatively large vacuoles, (Figure 125). In other cases there is created a complete or an almost complete track in the/

the vessel wall leading into the perivascular tissues. (Figures 129-30-1) Such a track may communicate directly with the vessel lumen, when there has been a disappearance of the lining cells. In other cases the endothelium may still persist, and it is often seen to be bulged towards the vessel cavity. In fact the appearances which I have described seem to demonstrate beyond doubt that in the dropsical infiltration of the vessel wall and tissues there must be in operation an influence similar to that responsible for the same changes as found in the innermost part of the vessel wall. This influence we have seen to be dependent on tissue alterations accompanied with the liberation of crystalloidal elements and the production of an enhanced osmotic tension, with a diffusion of fluid from blood to tissue in an attempt to re-adjust the discrepancy in the osmotic pressures.

The process of fluid imbibition is, as already stated, exhibited by the endothelial cells in a manner, which is almost diagrammatic in its clearness. In them we have demonstrated with precision the mechanism which, I believe, dominates the whole process of the oedematous escape from the vessel/

vessel lumen across the vessel walls into the surrounding tissues, and which, in the finer vessels is readily followed by an exodus of the blood corpuscles. In the description of the changes in the vessels of the pregnant tube, which it will be noted, are identical with those at present under discussion, I have already pointed out, that we are furnished with confirmatory evidence of the truth of this interpretation of the phenomena in the changes which are seen in the connective tissue cells. These were seen to exhibit the process of fluid imbibition in a manner similar in every respect to that occurring in connection with the endothelial cells. In the uterine wall, in the case of chorion-epithelioma, it is likewise easy to find that the intracellular fluid accumulations are not confined to the endothelial layer. In Figure 125 is shown a vessel the endothelial cells of which are swollen up in the manner described. In the wall are seen two connective tissue cells, which exhibit, in a like manner and in a like degree, the intracellular fluid vacuolation. It will be noted that here again the nuclei are displaced to the periphery of the cell where they have been flattened out by the accumulating fluid. The same change is detected in the outlying connective tissue/

tissue cells. (Figure 132-3). As described in the wall of the pregnant tube in two adjacent connective tissue cells the intracellular spaces filled with the imbibed fluid may flow together, leading to the production of a correspondingly large cavity bounded by the remains of the two cells. By the inclusion of a third cell in the process we obtain a space bordered by three cells, and so the process may extend till ultimately we have large oedematous spaces, occupied by fluid which is obviously derived by an osmotic diffusion from the adjoining vessel or the connective tissue spaces. These facts seem to me to prove beyond the least doubt that, at any rate, in the transference of the fluid to the tissues, osmotic phenomena play an important rôle.

So far our remarks have been limited, for the most part, to the thicker vessels. The resistance which their well-supported walls present to the fluid escape has resulted in a forcing into prominence of the actual details of the process. The same description of the changes applies with equal force to the fine vessels. Here, as can easily be understood, the oedematous ploughing up of the adjoining tissues is, on the whole, much more evident, and there is more apt to be a leakage of the corpuscular/

corpuscular elements of the blood. In the case of the thicker vessels even a small haemorrhagic escape is found only comparatively seldom. Where this has occurred to any marked degree, it is almost invariably from a fine vessel. In the fine capillary vessels the stages of the process are often more difficult to follow - this is entirely dependent on the fact that with the onset of the endothelial and tissue changes there is permitted an early and an easy exudation of the fluid, which escapes leaving little trace of the steps of the process behind it. That the same process is, nevertheless, in operation here also, I have been repeatedly able to determine by the discovery in the early stages of the same fluid swelling of the cells of the endothelial layer. The giving-way of the fine cell films in such a case at once creates a direct communication between vessel lumen and tissue space, and thus determines the possibility of an easy mode of escape for the blood corpuscles.

In connection with the smaller vessels there is another change of considerable importance, and one which was exhibited by the finer vessels of the pregnant tube. This consists as I have shown, in a gradually increasing expansion of the vessel wall, /

wall, so that a vessel of capillary dimensions may ultimately attain the size of a large sinus-like cavity. The details of this process will be referred to more particularly in the next section of this research.

It was noted in connection with the changes exhibited by the wall of the pregnant tube that the muscular tissue undergoes a progressive disintegration especially in the neighbourhood of the foetal elements, until it ultimately becomes represented by a homogeneous, faintly staining mass, in which all resemblance to the original muscle fibres is lost. The connective tissue cells, on the other hand, resist the process to a marked degree, and, even in the immediate proximity of the ovum, they may be recognised with well-preserved nuclei. In most places they were found to be enlarged, both in nucleus and cell body, and often in a way which identified them with the decidual cells of the uterine mucosa in the case of an ordinary pregnancy. Exactly the same description applies to the connective tissue cell of the muscular wall of the uterus in chorion-epithelioma. The same preservation of the cells is observed, and in many places they are found to enlarge in a manner closely resembling/

resembling the normal decidual cells. These changes will be referred to in greater detail in a subsequent section of this research devoted to the histology and functions of the Decidual Membrane.

The investigations which I have just recorded would seem to demonstrate beyond cavil that the transmission of the fluid from blood vessel to tissue is dependent on protoplasmic changes which are set in action by the presence of the chorionic elements. The part played by the endothelium and the connective tissue cells in the process is easily demonstrable. That the remaining elements composing the uterine wall, namely the muscle, contribute their share to the process can hardly be doubted. It has been seen that, especially in the proximity of the tumour cells, there is present a marked degenerative change in the muscle fibres. They swell up, their contour becomes obscure, the nuclei disintegrate and there is produced a homogeneous, structureless material. There is present, especially in the neighbourhood of the foetal cells, a gradual thinning out and disappearance of this fibrinous mass. That the removal of the muscle fragments is due to a direct absorption or phagocytosis on the part of the chorionic cells is unlikely. In none of my sections is there/

there any evidence of this process. In this respect my specimens entirely coincide with those of Teacher. The fact, moreover, that the softening and disappearance of the remnants of the muscular tissue is found at a considerable distance from the tumour cells would tend to indicate that some other process must be advanced to explain the phenomena. It seems to me certain that there has been induced by the chorionic activity a change in the muscle fibres which culminates in a breaking up of their substance and a subsequent solution of the products of disintegration. What these products are we are again unable to state with certainty. The fact, however, that I have frequently been able to detect in my specimens changes in the muscle fibres which coincide in every respect with those exhibited by the endothelial and the connective tissue elements, would indicate that with the progressive degeneration to which they are subject, we have associated chemical protoplasmic changes of the same order. In Plate XVII is represented a condition exhibited by the muscle fibres in my sections. There has taken place an absorption of fluid which has accumulated in definite vacuoles in the cell substance, and has displaced this in an outward direction. Here again we/

we have obviously the same osmotic phenomena in evidence, phenomena which are amenable to one explanation and one only, namely that in association with the muscle changes there has occurred a liberation of crystalloidal elements, with a consequent osmotic diffusion into the interior of the fibre. These changes are again exhibited in all degrees. With them, however, as we have indicated, there is apt to be a speedy disappearance of the muscle substance, which seems to pass into solution with great readiness. This fact, in all probability, explains why in my sections the actual process in operation is apt to be quickly obscured. (Plate XVII.)

We are thus furnished with evidence in favour of the belief that in the dragging of the fluid into the tissues the disintegrating muscle plays a part. The appearance just noted will be seen to coincide in many respects with the changes which are well-known to occur during the digestion of muscle etc., in vitro.

Recent research on experimental lines would seem to indicate that the chorionic structures are provided with an enzyme or enzymes which have the faculty of digesting muscle etc., and of transforming their protein/

protein constituents into substancescrystalloidal in nature. If this evidence be trustworthy we are supplied with information of a most convincing kind in favour of the conceptions I have advanced above.

Our histological investigations, then, have furnished us with evidence which points to the fact that in response to the influence of the foetal cells there have occurred widespread chemical alterations in the cells which are accompanied with an elevation in their intracellular osmotic tension. These changes, we have now been able to discover, are exhibited by all of the three important cellular elements of the uterine wall,namely the endothelium, the connective tissue and the muscle cells. The fluid escape,which these changes induce, is sometimes easily traced by stages from the innermost portion of the vessel wall, through the outer part and ultimately into the tissues. In some cases, however, the immediate environment of a vessel, which has resisted the teasing-out of the wall thus caused, is found to be the seat of a well-marked oedematous infiltration. In such a case we are, I think, justified in thinking that the colloidal membrane essential to the process has been formed by the entire thickness/

thickness of the wall, which in these instances is usually especially compact. In the other condition, where the fluid has gradually leaked through the wall, leaving its track behind it, the colloidal membranes have been formed by the successive parts of the vascular wall. These are apt in the process to give way, probably in a manner which I have indicated in connection with the Pregnant Tube. When such occurs we have the production of a breach in the wall, through which the corpuscular elements may escape. In Figure 128 is shown the earliest stage of the process. Here the blood has passed into the vessel wall and has accumulated under the uplifted endothelial sheet. Though there is no gap visible in this figure, it would seem likely that for the passage of the corpuscles from one region to another a complete breach is essential. In this vessel it is probably present at another level. The next stage of the process I have indicated on Plate XVI. Here the fluid infiltration has resulted in a teasing apart of the walls to the extent of permitting an escape of the red cells into the media. In some instances the red cells may be followed a stage further, i.e. through the vessel wall into the adjoining tissues. (Plate VIX.). This is especially evident in the proximity of the foetal elements and, on the/

the whole, except here, is a condition of rarity in vessels of any thickness. Throughout the uterine wall there is, even at a distance from the tumour cells, a more marked haemorrhagic escape from the finer vessels. (Fig. 132.).

Enough has been said, I think, to indicate that the leakage of the red cells is dependent on the dropsical exudate. In fact the escape of the fluid constituents of the blood must be considered, in the light of the above-recorded investigations, as the precursor of the escape of the more solid elements. How is this actually accomplished? Is it due solely to the fact that the breaches created in the vessel walls have permitted a mechanical extension of the red corpuscles, or is it the case that the sucking or imbibing of the fluid from the vessel lumen is associated with a continual stream from the vessel, which, after the breaking down of the tissue barriers in the way we have indicated, at last drags out the blood cells? That this may occur is rendered probable by the fact that the fluid tracks can be traced, often with distinctness, to extend from a vessel through a large territory of the uterine wall. This is not unlikely to be explained by the fact that in its progress into regions of continually higher and higher/

higher osmotic tension there is induced a constant streaming from the vascular lumen. Whether we have to deal with the former process, namely the vis a tergo, or the latter, the vis a fronte, it is, however, impossible to assert with precision. From what we have observed, however, it seems not unlikely that the latter must play an important part. It, moreover, explains how the immediate surfaces of the chorionic masses are often bathed in maternal blood. The tissue changes are more and more marked as we approach the foetal cells, and reach their maximum in the immediate proximity of these elements. This would imply that there is produced a gradient of osmotic tension rising, probably rapidly, to the chorionic surface. This would result in a streaming of the fluid and corpuscles towards the chorionic surface from the vessels in this region. (Plate XIV.).

It would seem not unlikely that an additional factor tending to lead to an attraction of the blood to the chorionic surface is to be found in the fact that the foetal cells must be actively imbibing the tissue fluid in their immediate proximity. This would result in a keeping up of the flow from behind and an ultimate flushing of the surface with red cells whose numbers would tend to increase as more and more/

more of the fluid was hurried forward to supply the wants of the chorionic cells. The evidence which we have in the shape of a structural adaptation of the chorionic surface for such a process of active imbibition will be touched on in a subsequent section of this research.

I have adduced sufficient evidence to indicate that in the escape of the fluid and red cells from the vessels at a distance from the foetal elements there must be in operation something more than a mere mechanical extension through the vessel walls. In view of the fact that I have entered fully into this point in my description of the changes in the pregnant tube, which are similar in every respect to those described here, I have deemed it unnecessary to re-open the discussion in full on this occasion. After what has been said it will be clear, I think, that so far from the facts being accounted for by a squeezing of fluid from the vessels, where it is under an increased pressure, the fluid which escapes into the tissues is actually under a hydrostatic pressure in excess of that exercised on the vessel walls. In proof of the fact that this is not dependent on a vital or, at any rate, a secretory activity on the part of the endothelial cells, I would/

would again refer the reader to the manner in which this possibility was disposed of in connection with the section devoted to the changes observed in the pregnant tube. The vacuolation of the endothelial cells here again is in all probability not an indication of a specialised functional activity; but merely an incident in the changes which are responsible for the fluid transmission. This being so, we are left, in our quest after the secret, to alterations in the tissue elements, and enough has been said, I maintain, to indicate the probable nature of these changes and the manner in which they act.

OTHER CHANGES IN THE THIN-WALLED VESSELS.

As already noted, round the fine vessels there is a well-marked oedematous exudate, with, in many places, even at a distance from the chorionic cells, a haemorrhagic escape. In many instances one can detect the red cells streaming through the thin walls into the adjoining tissues. This is, for the most part, especially evident in the proximity of the ovum. It is often well in evidence where there are within/

within a considerable distance no cells in the least resembling the chorionic elements. It is, in all likelihood, dependent on the tissue changes to which I have already referred. In the near proximity of the foetal cells it is often possible to detect a greater exodus of the red cells on that aspect of the vessel which is nearest the site of the tumour invasion. Here also the oedematous ploughing up of the surrounding tissues is often more marked than round the rest of the vessel circumference. These phenomena must depend on the fact that the tissue changes, which result in a liberation of crystalloidal elements, are determined by some influence emanating from the foetal cells, and which is more and more marked the nearer these are approached. The greater blood escape from the vessels nearest the ovum is thus easily understood. It obviously is to be interpreted as an explanation of the mode in which the surface of the foetal masses are, during their advance into the uterine wall, kept continually bathed in the maternal blood (fluid and corpuscles) from which they abstract their nourishment. An attempt will be made in a later section to demonstrate that the process just described constitutes the chief mechanism, and, in all probability, the/

the only mechanism by which the foetal masses are furnished with their pabulum in the shape of the maternal blood. A direct infiltration of the vessel walls is to be looked upon merely as an incident in the process of the foetal invasion and possesses no more importance than that associated with the manner in which the other maternal tissues are opened up and destroyed.

In Plate XIV is represented the conditions typically present. On the upper aspect is seen a mass of tumour cells, with large nuclei. The muscle in the proximity is in places markedly degenerated. Lower down a long thin-walled vessel is seen surrounded by a haemorrhagic escape. There are no cells in the least resembling chorionic cells in the immediate proximity with the exception of a large darkly staining cell with two nuclei. Whether this is foetal or maternal it is impossible to say with certainty. The plate demonstrates beyond doubt the existence of the blood leakage without a direct invasion of the walls. It is taking place not only towards the foetal mass but also into the tissues on the remote aspect, due to the tissue changes I have referred to. On the right side there are appearances which suggest that a new capillary formation is occurring. Whilst the/

the exact changes are obscured in this vessel for a reason I have mentioned, they are clearly discernable in the thicker vessel on the lower aspect. Here on one side there is seen a marked swelling of the tissues on the inner aspect of the wall, obviously due to an active fluid imbibition.

The same changes are also well seen in Plate XV. Here there is a haemorrhagic escape from the small vessels before the actual foetal invasion has reached them. The same endothelial changes are present. This plate also shows at one place the wholesale opening out of the wall of a vessel before the arrival of the chorionic elements. In this way the vessel lumen actually advances to meet the invading cells. Here the process is clearly due to a solution and giving-way of the vascular and surrounding tissues.

In the proximity of the smaller vessels there is, in many places, a marked leucocytic emigration into the tissues. I have not been able to discover in my sections that this is most marked in the neighbourhood of the chorionic cells. It is often distinctly marked at a long distance from these. The leucocytes are chiefly of the polymorphonuclear type.

Besides the vascular changes associated with /

with an increased fluid and corpuscular escape, there are other alterations of considerable interest and importance. These fall into two classes. In the first place, scattered throughout the uterine wall there has occurred the formation of large sinus-like expansions of the fine-walled vessels, the walls of which are formed by a single endothelial layer. In the second place, there is found in some places the formation of new capillary vessels. We thus note that in this respect the changes in the thin vessels coincide with those which I have described in connection with the wall of the pregnant tube. The actual mode of production of these sinuses and new vessel branchings, also, would seem to conform in every detail with that which I have recorded in connection with the pregnant tube. My specimens of chorion-epithelioma unfortunately do not permit of such a perfect study of the cellular changes responsible for these vessel alterations, which, we shall remember, were demonstrated in some of my sections of the pregnant tube in a manner which was almost diagrammatic in its clearness. In some places, however, we have the successive steps in the two processes exhibited in a way which leaves little room for uncertainty./

uncertainty.

Here again the two changes, the vascular expansion, and the new vessel formation, are probably dependent on the same common factor, namely the cellular alterations which we have noted to occur throughout the uterine wall. I have, in a preceding page, referred to the fact that, in many places, the endothelial cells and the connective tissue cells are distended with fluid imbibed as the result of some protoplasmic changes which have determined an increase in the intracellular osmotic tension. These changes we have seen must, in some way or other, be dependent on the chorionic activity and they must be associated with a liberation of crystalloidal elements. They are widespread throughout the wall of the uterus.

MODE OF FORMATION AND STRUCTURAL CHARACTER OF FINE-WALLED SINUSES.

In this section I wish to refer to the sinus-like vessel expansions, which are scattered about the uterine wall. Their boundaries are formed by a layer of flattened cells. In size they exhibit great variation. Some are comparatively small, whilst/

whilst others have in their formation extended through a large territory of the uterine wall. They vary greatly in shape. In some places they possess a uniformly circular or oval contour. For the most part, however, they have irregular boundaries. In many cases their outlines are extremely uneven, and the shapes assumed would seem to be determined to a large extent by mechanical influences. Thus they are often seen to skirt muscle bundles or to insinuate their way between two muscle masses. In this way there are often produced marked differences in their diameter at different parts of their course. Where there has been an obstacle to their expansion they have remained narrow, sometimes with a width not more than that of a fine capillary. Beyond the mechanical obstruction they again expand, only, perhaps, to become attenuated at a further part of their course. (Figures 136-143). For the most part their number and size are greater the nearer the chorionic elements are approached. It will thus be seen that in their characteristics they closely resemble similar structures which I have described in the wall of the pregnant tube. They likewise correspond closely to the sinus like expansions which/

which are found in the uterine wall during an ordinary pregnancy. It would seem more than likely that in their formation they must conform with these, and for this reason any light which I can cast on their mode of production will probably apply to the pregnant uterus.

The way in which the expansion of the wall of such a space is brought about is sometimes clearly discovered by a close study of the cellular changes in the endothelial lining and the immediately apposed to connective tissue cells. Where a vacuolated connective tissue cell lies against a vacuolated endothelial cell there is apt to be an amalgamation of the cell spaces. The fluid imbibition in each case must depend on a chemical alteration in the protoplasm of the cell with the production of an enhanced intracellular osmotic tension. The exact manner in which the fusion of the two cell spaces occurs it is difficult to say. Is it due to a disappearance of the cell membranes intervening between the fluid spaces of two entirely distinct and independent cells, or is not rather merely due to a passage along and expansion of the protoplasmic communications which we can often detect passing between the endothelial and the connective/

connective tissue cells? We have already seen that this latter explanation in all probability accounts for the creation of the longitudinal fluid tracks which is often seen to be formed by similar changes in connective tissue cells, which are placed end to end, and it also explains the manner in which two such altered connective tissue cells which lie side by side amalgamate to form a more or less circular space bounded by two cells. However formed there can be little doubt that the fusion of the fluid vacuoles of the endothelial and the connective tissue cells results, subsequent to a disappearance of the dividing inner cellular film, in a carrying outward of the vessel lumen to a corresponding extent. By means of this process there is rendered possible a gradual extension of the boundaries of the sinus till it may reach the proportions we have indicated. If the change occurs uniformly all round the circumference of the blood space there is a symmetrical and equal increase in the diameter. If, however, a muscular bundle or some other obstacle becomes interposed in its path of advance, the increase in that part becomes impeded with the result already noted. We see then that this process of vessel expansion is determined by two factors, firstly the osmotic changes in/
in/

in the cells and, secondly, influences which are purely mechanical in nature. It is interesting to note how the expansion occurs at the expense of the surrounding connective tissue cells, which have the faculty of ranging themselves into line to form an endothelial layer. This fact would seem to indicate in the clearest terms the existence of a close structural relationship between endothelium and connective tissue cell.

NEW VESSEL FORMATION.

In none of my specimens of chorion-epithelioma have I been able to discover this process to the extent in which it was exhibited in the wall of the pregnant tube. Where present, also, the steps of the process are never delineated in the convincing manner visible in the wall of the tube. The fact that I have been able to demonstrate the same endothelial and connective tissue changes, and the fact that in its results the new vascular formation is the same as in the former site, suggests that the same protoplasmic changes may be the determining factor here also.

IS/

IS A DIRECT INFILTRATION OF THE VESSEL WALLS BY
THE CHORIONIC CELLS THE CAUSE OF THE
BLOOD ESCAPE?

I have in several places referred to the fact that according to Teacher and others the tumour masses in the case of chorion-epithelioma are furnished with their supply of maternal blood only after they have invaded and opened up the uterine vessels. The destruction of the vascular wall is followed by a mechanical escape of the contained blood which then flows over the surface of the foetal masses. The bathing of the foetal cells by maternal blood is also according to these observers determined to a smaller extent by the fact that after working their way through the vessel walls the tumour cells may spread along within the vessel lumina, either lying free or attached to the inner aspect of the wall.

With regard to the occurrence of this latter process I am in entire accord with the above-mentioned observers. I have often noted it in my sections. I am inclined to believe, however, that from the point of view of affording an explanation of the manner in which the chorionic cells come into contact with the maternal blood it occupies a position similar to the process/

process by which the surface of the villi which bore their way into, and spread along, the maternal vessels (probably veins) in the uterus in ordinary pregnancy, and in the pregnant tube, come to be bathed in the maternal blood. In other words it must be considered to play a part of comparative unimportance; only the regions of the chorionic masses projecting into the vessels can in this way and without some other mechanism be supplied with their nourishing fluid. Is this other mechanism to be sought for in the fact that the breaches created by the chorionic cells in the walls of the vessels permit a wholesale escape of the contained blood by virtue of the intravascular pressure?

The conclusions which I have come to on this subject are best summarised by repeating what I have several times stated, namely that the extension of the chorionic elements through, and into, the vessels is to be considered not as a feature of the process which is essential to the growth of the tumour masses, but rather merely as an incident in the invasion of the uterine wall by the foetal cells.

In many places the tumour cells are found to have replaced the tissues forming the vessel wall and are seen to project, usually by a fairly extensive/

extensive surface, into the vessel lumen. (Plates XIV - XV). In other places one can see the foetal cells approaching the vessel but still separated by a portion of the uterine wall from the lumen. (Figure 136.). Across this intervening septum it is often possible to detect the streaming of the red cells towards the tumour elements and this even when the vessel confines are still apparently intact, or at any rate certainly before any of the chorionic cells have extended as far as them. (Plate XIV).

At the same time the maternal tissues are usually spread apart by an oedematous infiltrate. These observations, which I have been able to make in all my sections with the utmost certainty, prove beyond doubt, as already stated, that for an exodus of the fluid and corpuscles a direct infiltration and destruction of the vascular walls is not essential. Where this process is encountered it must be regarded merely as incidental to the general invasion of the uterine tissues by the foetal structures.

In connection with this spread of the tumour cells into the vessel lumen there are some appearances which tend to indicate that it does not consist in a mere passive destruction and replacement of the vessel walls by the invading tumour cells.

In/

In many places I have been able to detect a gradual opening up of the vessel walls and advance of the blood cavity thus produced through the maternal tissues to meet the chorionic masses.

We shall better understand what occurs on these occasions by a study of the changes which occur in the walls of a vessel into, and along, which a mass of the tumour cells have grown. As we have already noted this is a condition usually not difficult to find in a section of the uterine wall which is the seat of a chorion-epitheliomatous invasion. The same changes are detected where an embolus of the tumour cells has lodged within a maternal vessel. As has been pointed out by Teacher, in such a case there is apt to be a gradual expansion of the vessel, which may attain a diameter greatly in excess of that of the contained tumour mass. In this change Teacher rightly sees an analogy to what occurs in the pregnant uterus, where, as is well-known, there is a gradual recession of the uterine mucosa before the foetal elements. This provision, which is essential to the formation of the intervillous blood space, results in the production of a gestation cavity in size greatly in excess of the dimensions of the contained/

contained ovum. I have referred to the same change in the wall of the pregnant tube. In the account of the changes which were present in the uterine mucous membrane in the case of their early embryo, Bryce and Teacher¹⁸ somewhat amplify the original observations of the latter writer. In page 42 of that publication they make the following statement. "We may here digress for a moment to point out a very suggestive analogy with the normal ovum in respect of its influence on adjacent maternal tissues, presented by an embolus of chorion-epithelioma in its development into a secondary tumour. The embolus, usually somewhat larger than the imbedding ovum, lodges in the fork of a blood vessel, the wall of which soon shows degenerative changes identical in character with those seen in the decidua around the present ovum. These occur prior to the invasion of the tissues by the tumour cells. The injured blood vessel dilates into a more or less globular aneurismal cavity, and there may be considerable growth of the embolus in its interior before invasion begins. The blood in the neighbourhood of the embolus does not coagulate until secondary changes, which need not be discussed here, bring about that result. After a time the tumour elements invade the maternal tissues and the embolus becomes attached./

attached. At this stage appearances may be found very similar to those around the margin of Peter's ovum.

The formation of the aneurism with its necrotic wall round the embolus finds a parallel in the behaviour of the decidua round the human ovum. We may assume that, as in the case of the guinea-pig ovum, there is primarily destruction of a fairly wide zone of tissue, which draws away from the ovum partly, at least, on account of the swelling which accompanies coagulation necrosis. The shed blood must further stretch the soft decidua just as the wall of the vessel is stretched into the wall of an aneurism, and the necrotic zone of the decidua is removed, like the necrotic wall of the aneurismal sac, before attachment can take place. Also, as in the case of the embolus, the necrosis is at first progressive, but soon, reaction taking place in the surrounding tissue, it becomes more capable of resistance, and consequently of effecting a union with the trophoblastic processes, as will be described later".

These remarks of Bryce and Teacher indicate clearly the close resemblance between the effects of the chorionic cells on the maternal tissues, whether it/

it be in the case of an abnormal development such as in the condition we are at present considering, or in the case of the normal ovum imbedded in the uterine mucous membrane. It would seem clear that an understanding of the maternal changes responsible for the gradual expansion of a vessel, in which a chorion epitheliomatous mass is lodged, will probably help as in our attempt to solve the secrets underlying the manner in which the uterine mucous membrane reacts to the growing ovum under ordinary circumstances.

In his description of the changes by which there occurs a gradual expansion of the walls of a vessel within which there is lodged a tumour mass, Teacher has confined his attention to those vessels in whose walls there is present a marked degenerative change. In many of my sections I have been able to note an aneurismal expansion of vessels containing a clump of the foetal cells, in which the walls are formed by a complete layer of flattened cells. In some places this expansion of the vessels has occurred to an extreme degree and apparently in response to the activity of a comparatively small clump of the tumour cells. (Figures 139-140). Such a blood space corresponds in every respect to the sinuses which we have seen to be scattered through the muscular wall of/
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of the uterus. These I have pointed out are formed not by a gradual mechanical giving way of degenerative tissues, but by a process in which active changes in the endothelial and connective tissue cells are seen to take a prominent part. These changes, which must be dependent in some way on the chorionic influence, result in a gradual invasion of the surrounding tissues by the expanding blood cavity, and are associated with an incorporating within its walls of the altered connective tissue elements. These I have shown are endowed with the faculty of ranging themselves into line with the original intimal cells and of thus forming a new endothelial layer. This process of vascular expansion is dependent on the intracellular changes which are responsible for many of the phenomena associated with the presence of the foetal elements. These so alter the chemical composition of the cell substance as to determine an imbibition of fluid with a vacuolation of the cell body. In many cases this process culminates, especially in the case of the degenerating muscle, in which the same changes are visible, in a wholesale transformation of the cell substance into materials, which pass into solution in the imbibed fluid.

Does the aneurismal expansion of the vessels, /

vessels, to which we have referred, demand the introduction of a process different from that just mentioned and which, I have shown, suffices to explain the sinus-like vascular distension in other places? As the results are similar in every respect, with the exception of the fact that in the vessel with the embolus or tumour extension, the immediate proximity of the chorionic elements has resulted in a greater degree of expansion, it would seem probable that in each case we are dealing with exactly the same phenomena. That this is actually the case I have been convinced by a study of the changes in the endothelial and adjacent connective tissue cells round the margin of such an expanding vessel. One can often detect the results of the same osmotic changes to which I have repeatedly called attention. (Plate XV, lower part). In most places where the maternal tissues have receded from the chorionic cells, the degenerative softening changes have obscured, often quite beyond recognition, the actual steps of the process. Here again, however, we can sometimes detect, through the veil cast over the changes by the disintegration present, exactly the same process in operation. In the case of a thicker walled vessel in which the same process may be found, the muscular tissue present is often/

often so markedly degenerated as to render a satisfactory study of the successive steps of the change impossible. In all the various types of vessel involved in the process of progressive expansion in consequence of the chorionic activity it is, however, possible in many places to distinguish the fact that we have in operation factors other than those suggested by Teacher. Again we can determine the existence of a direct fluid imbibition by the tissues. We see a swelling up of the endothelial and connective tissue cells, and often also of the muscle fibres by (Plate XV and figure 146). fluid derived from the adjacent blood lumen. In fact we can often discover with certainty that as before, the opening up of the tissues by the fluid is determined by osmotic changes in the tissue elements, changes, moreover, which result in a teasing asunder of the vessel boundaries by a force greater, and probably much greater than that of the intravascular pressure. After a separation of the inner portion of the wall occurs, the constituent elements are so opened out that in this region we lose sight of the process completely. It can now, however, often be seen advancing in the same way into the more external structures. These, in their turn, become opened out and/

and displaced in the same manner, till ultimately we may have produced a blood space vastly greater than that originally present. That this may occur is demonstrated by finding the blood channel shrinking often to meagre dimensions immediately beyond the region of the tumour mass. The difference between this process and that which results in a more or less uniform expansion of the vessel wall, will be seen to be one more apparent than real. In each case the predominating influence is a change in the tissue elements, which determines an active absorption of fluid from the vessel lumen. In these phenomena we have exemplified a fact of considerable interest and importance, namely that the presence of the tumour elements, under some circumstances, besides leading to changes which determine a flow of the blood constituents towards their vicinity may so act as to result in a streaming away of the fluid (and sometimes of the corpuscles) from the position which they occupy. I mention this fact, because it seems to me to demonstrate in a convincing manner the important rôle which alterations in tissue composition play in the transference of the blood from vessel to adjoining structures.

In many cases such expansions of the tumour-containing/

tumour-containing vessels may occur in an extremely irregular manner - instead of being more or less smooth in outline the resulting blood space may exhibit an irregular and ragged margin. This depends on the process having involved some parts of the wall more than others. (Figure 146).

In addition to this simple imbibition of fluid by the endothelial and connective tissue cells, which subsequently become displaced in an outward direction, there are other changes of considerable importance, which are exhibited in such an aneurismal formation in the course of the affected vessel. Here again there is found a thinning out and disappearance of the tissue elements, especially involving the muscular fibres. These, as I have pointed out on a preceding page, after exhibiting alterations which point to the fact that they are the seat of katabolic changes, associated with the liberation of crystalloidal elements, soon undergo a progressive softening and breaking up, and ultimately disappear altogether. This can be explained only by assuming that the chorionic influence has led to a sort of digestion of the fibres, which then pass completely into solution in the imbibed fluid. The same changes are sometimes seen, though never to anything like the same degree in the connective tissue elements.

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In view of these investigations I venture to assert that the gradual expansion of the affected vessels in an aneurismal manner is dependent, in the main, on factors which have hitherto escaped detection. In the first place as the result of the chorionic influence we have changes in the tissue cells by which there is set into action an imbibition of the blood fluid. The steps of the transference of this fluid into the tissues can often be traced with ease. It naturally, to begin with, is most evident in the immediate proximity of the source from which it is drawn, i.e. the vessel. The walls of this are gradually teased out and in some cases dissolved. This process working its way outwards by more or less easily recognised stages may ultimately lead to the production of a relatively enormous blood space, the boundary of which is often ragged in appearance. We thus see that the next essential to the occurrence of this vessel expansion is the blood fluid. If our conception of the changes be correct this acts not by virtue of the hydrostatic pressure existent in the vessel, but is essential merely for the completion of the intracellular changes and the dissolving process which underlie the ultimate giving way of the vessel wall. I have stated/

stated that the intravascular pressure in all probability takes a comparatively unimportant share in the production of the changes. I make this statement advisedly because in many cases I have been able to convince myself that the changes have been determined apparently in their entirety by the osmotic alterations in the tissues. In this respect my present investigations coincide with those made on the way in which the vessels open up in the wall of the pregnant tube.

So far we have been concerned with the expansion of the vessels into aneurismal cavities as it occurs in response to the influence of a tumour mass contained within the corresponding vessel. It is often possible to detect changes exactly similar in vessels which do not contain such embolic or extension portions of the chorionic clumps. We have already referred to the fact that throughout the uterine wall there is evident, even in the thicker-walled vessels, a process of teasing apart of the endothelial and muscular layers. Only rarely does this culminate in a complete giving way, but it must be considered as similar in nature to the process to be immediately described. This change in the thicker vessels as we have noted is most marked in the immediate/

immediate proximity of the ovum.

In the poorly supported vessels, and especially in vessels whose walls consist merely of an endothelial layer, these oedematous changes often result in a wholesale separation of the constituent elements and an expansion of the blood cavity at the expense of the surrounding tissues. In many cases this takes the form of a more or less uniform distending of the vessel, which in the process continually adds to its endothelial layer, which throughout remains complete, the connective tissue cells which are encountered. This change results, as I have demonstrated, in the formation of the sinuses which are richly scattered throughout the muscular wall. In other cases, however, the expansion is more irregular in nature and results in the production of a space with an uneven and often very ragged outline apparently still in the process of burrowing into the surrounding tissues. This change is entirely comparable in its nature to that which leads to a similar expansion of vessels in which parts of the tumour are located. On Figures 145 & 147 are shown such spaces; - we note the irregular contour which they exhibit and we observe how arms of the main cavity are being projected into the surrounding tissues./

tissues.

After this description of the vascular changes, which though varying greatly in their results, are dependent on the same fundamental cause, we are now able to understand the appearances often presented by a vessel when a clump of the chorionic cells is advancing towards its neighbourhood. I have already referred to the fact that the manner in which the foetal elements reach the intravascular lumen is not wholly due to a simple destruction of a vessel wall, which, in the process, acts a part entirely passive in its nature. We can understand how an appearance which is frequently observed, namely that, before any of the foetal cells actually reach the vessel, the walls of this often become teased out and, especially in the case of a thin-walled vessel, may virtually advance through the tissues to meet the invading cells. (Figures 136-7 and Plate XV). The process underlying this remarkable phenomenon is exactly the same as that which determines the expansion both of the tumour-containing and the tumour-free vessels, and is determined by the chorionic activity which sets into action the tissue changes, to which I have often referred. We thus discover that the passage of the blood cells and fluid across the tissues which intervene/

intervene between the advancing tumour masses and the neighbouring vessels, and the opening up of the vessel walls before the invading foetal cells are dependent on the same common factor. The giving way of the vessels in this way is often most evident on that side of the vessel which is nearest the chorionic cells. (Plate XV), and still before there has occurred a projection of even isolated foetal cells as far as the vessel wall. It is, at first sight, rather remarkable to note that the same opening out of the vascular wall has often occurred also on the more distant aspect. In view of what I have said with regard to the vessel changes in general we should, however, have no difficulty in understanding the rationale of this.

SUMMARY OF VESSEL AND TISSUE CHANGES IN CHORION-EPITHELIOMA.

By a study of the histological changes which are induced in the uterine wall by the presence of the chorion-epitheliomatous masses we are thus enabled to draw the following conclusions:-

- (1) The chorionic influence in some way or other determines the occurrence of protoplasmic changes/

changes in the cells, which lead to their imbibing fluid which can often be seen to have accumulated in the cell body under a hydrostatic tension clearly higher than the pressure of the intravascular blood and of the fluid in the surrounding tissue spaces. This we have seen can be explained only by assuming the occurrence of some chemical alteration in the cell substance which is associated with the liberation of crystalloidal elements. These raise the osmotic pressure of the cells and lead to a diffusion of fluid across the colloidal membrane formed by the cell protoplasm. These changes we have noted without the least possibility of doubt in the endothelial cells and in the connective tissue cells. In many places we have been able to detect an exactly similar process in regard to the muscular fibres. In other words, all the cellular elements of the uterine wall are involved in these protoplasmic changes. The exact nature of these chemical alterations is so far still beyond/

beyond our grasp, but as to the effect which they produce we are left little room for doubt.

In this section of my researches I have, to obviate the necessity for constant repetition, been content with merely mentioning or, in some instances, leaving to be understood, many of the changes to which I have referred in greater detail in the discussion of the changes exhibited in the uterine mucosa and in the wall of the pregnant tube.

- (2) These changes are responsible for the well-marked oedematous infiltration from the vessels which characterises the uterine tissues in a case of chorion-epithelioma. They, moreover, amply account for the blood escape from the vessels into the neighbouring tissues and towards the chorionic surface. This is dependent on active tissue changes which determine a sort of suction into the tissues of the maternal blood.
- (3) An escape of the blood by merely mechanical means from a broken down vessel wall does not/

not suffice to explain the manner in which the foetal elements derive their nourishment. On the contrary the foetal cells are often seen growing towards the site from which the blood fluid and corpuscles are flowing. The significance of this I have touched on in connection with the pregnant tube. The many and varying vascular changes which are seen are dependent on the same common factor, namely the above-noted tissue changes, which the foetal cells provoke. They explain the gradual expansion of the vessels both into endothelium-lined sinuses and into irregular and ragged spaces. Both conditions may occur with or without the presence of the tumour cells in the vessel lumen. Where the wall is uneven and disintegrating this merely indicates that the muscular (or sometimes the connective tissue elements) are succumbing to the influence causing the protoplasmic changes. Even here the expansion is probably due chiefly to an active fluid imbibition with a subsequent/

subsequent tissue displacement or solution.

DECIDUAL FORMATION IN THE UTERINE WALL IN CHORION-EPITHELIOMA.

In many of my sections there is a well-marked enlargement of the connective tissue cells of the uterine wall. This change is comparable in every respect to that seen in the typical decidual formation. I shall refer to these changes at greater length in a subsequent section of this research.

STUDY of the CHANGES in the MATERNAL TISSUES other than the UTERUS, which are the SEAT of CHORION-EPITHELIOMATOUS EMBOLI.

For this investigation I have had the opportunity of studying the changes as seen in the case of the lung. These correspond for the most part to the changes which I referred to in connection with the uterine wall. They have, in addition, afforded me the chance of observing the manner in which the embolic/

embolic masses of the tumour may be strangled and ultimately destroyed by the haemorrhage which they provoke. For a description of these changes I would refer the reader to the admirable paper of Teacher already mentioned.

In the lung I have been able to observe the blood exodus occurring in exactly the same manner as that described above. I have also been enabled to discover that here again sinus-like vascular expansions are produced by a process identical to that described in connection with the pregnant tube, and the uterine wall in chorion-epithelioma. (Figures 149 and 150).

THE/

THE CAUSATION OF OEDEMA, as EXEMPLIFIED by the
 STRUATING MUCOSA, by the WALL of the PREGNANT
 TUBE, and by the UTERUS in CHORION-

EPITHELIOMA.

The investigations which I have presented
 in the preceding pages, on so far as they have been
 concerned to a large extent with the histological
 changes in the tissues which accompany the production
 of an oedematous condition from the vessels, have been
 added as with information of considerable importance
 as regards to the process.

SECTION VI.

As already noted, in the chapter of the
 The CAUSATION of OEDEMA, as EXEMPLIFIED by the MEN-
 STRUATING MUCOSA, by the WALL of the PREGNANT
 TUBE, and by the UTERUS in CHORION-
 EPITHELIOMA.

of the capillaries. This may be due to a variety of causes, such as
 chemical changes which result in a condition of in-
 creased permeability (physiology) or to the action of a mechanical force
 of the individual cells (the physical cause of
 endothelial). In the past years we have seen a great
 deal of discussion as to the cause of the oedema of the
 tissues with liberation of the individual elements and
 the/

THE CAUSATION of OEDEMA, as EXEMPLIFIED by the
 MENSTRUATING MUCOSA, by the WALL of the PREGNANT
 TUBE, and by the UTERUS in CHORION-
 EPITHELIOMA.

The investigations, which I have recorded in the preceding pages, in so far as they have been concerned to a large extent with the histological changes in the tissues which accompany the production of an oedematous escape from the vessels, have provided us with information of considerable importance in regard to the etiological factors responsible for the process.

As already noted, in the escape of fluid from the vessels the possible causal agents are (1) an increase in intravascular pressure with a mechanical filtration through the vessel walls, especially of the capillaries, (2) the endothelial lining of the vessels: this may act by virtue of physical and chemical changes which result in a variation of permeability (physical) or by virtue of a secretory activity of the individual cells (the "vital" theory of Heidenhain). In the next place we have (3) changes in the tissues in the shape of protoplasmic alterations with liberation of crystalloidal elements and the/

the production of an osmotic diffusion stream through the vessel wall into the surrounding parts. In the production of an oedematous accumulation in the tissues we may have a pathological change involving one or more of the above agents which are concerned with the physiological lymph flow, and we may have, in addition, lymphatic obstruction with a consequent involvement of the channels by which the fluid is removed from the tissues. The influence of the last factor in determining the abnormal fluid accumulation in the tissues, I have been unable to ascertain with any degree of certainty. That it must play a part would seem likely; it is probable that the degenerative tissue alterations are associated with widespread involvement of the lymph vessels. The role enacted by this factor is, however, thrown into comparative insignificance by the discovery that, in the increased fluid accumulation, we have throughout the process, in a manner which is clearly distinguishable, a manifestation of changes which determine an exaggerated transference of fluid from vessel to tissue. It is with these that we are especially concerned in our present enquiry.

THE MENSTRUATING MUCOUS MEMBRANE.

Associated/

Associated with the blood escape during the process of menstruation we have a well-marked fluid infiltration of the tissues. This is most evident in the mucosa immediately prior to the onset of the menstrual flow i.e. in the premenstrual stage.

Under ordinary circumstances we have seen that the exact process in operation is difficult to decipher. The fluid and blood escape in the ordinary mucosa is associated with an opening up and displacement of the cellular elements of a homogeneous tissue which is efficiently adapted for such a process, by virtue of its soft, mobile nature. Under these circumstances it is sometimes impossible to state with precision whether the displacement is dependent on tissue changes or whether it is due to mechanical influences. I have shown, however, that, where there is a thickening of the vessel walls of the uterine stroma, we are furnished with information of an un-ambiguous nature in regard to the actual changes involved in the fluid escape. In this condition it was shown that a mechanical filtration from the vessels to the tissues failed to account for the histological changes present. To explain these changes we are forced to admit the existence of protoplasmic alterations which have/

have determined an active imbibition of fluid. This process, for reasons which I need not recapitulate, is not confined to the lining cells but is shared by the cells of the vessel wall and the surrounding stroma. In fact, as I have indicated, it would seem that in the mucous membrane of the uterus all the elements of the vascular wall and of the surrounding stroma possess similar structural characters, and simply correspond to poorly differentiated units of the homogeneous protoplasmic material of which the stroma is constituted. If this be actually the case it is impossible to recognise the existence of a specialised function on the part of the endothelial cells.

Whilst it was freely admitted at the time that it would be unwise to apply deductions drawn from a study of the process as seen in the case of the pathologically thickened vessels to the normal menstruating mucosa, the investigations which I subsequently recorded confirmed the conclusions which were provisionally formulated and it was shown that the structure of the stroma must be considered to be adapted for a ready imbibition of the blood fluid. The fact, that I have been able to advance evidence in connection with the study of the pregnant tube and the chorion-epitheliomatous uterus which clearly delineates the structural identity of the endothelial and the connective tissue cell, would seem to/

to lend support to the opinions I expressed regarding the structure of the stroma of the endometrium.

THE PREGNANT TUBE.

Here we were able to discover without doubt that in the escape of the fluid from vessel lumen to tissue we are confronted with a process which is dominated by endothelial and tissue changes. In consequence of the chorionic activity there occur protoplasmic alterations which are associated with an increase in osmotic tension and a subsequent abstraction of fluid from the vessels. These changes, I have shown, are exhibited with distinctness by all three main elements of the tubal wall - endothelium, connective - tissue and muscle. In this case we have to deal, especially in the muscle, with protoplasmic alterations which are apt to culminate in a progressive degeneration and disintegration. Here again the process of fluid infiltration is closely associated with the blood extravasation, which, in the proximity of the foetal cells, occurs to a degree which is excessive. Here again a vacuolation of the endothelial cells is to be considered as an exhibition of the changes which are, throughout the tubal wall, /

wall, responsible for the dropsical infiltration of the tissues. In fact, of such constant occurrence is this fluid imbibition by the lining cells in a vessel from which the fluid is escaping that I have been forced to the conclusion, as the result of my investigation, that it must be taken as indicative of some process in operation which is associated with changes that are conspiring to forcibly abstract fluid from vessel lumen to tissue.

CHORION-EPITHELIOMA.

Both in the regions of the primary invasion of the foetal elements and of the secondary malignant deposits, we have in evidence vascular and tissue changes in every respect identical to those above-mentioned. The dropsical infiltration of the maternal tissues, which characterises this condition, are again dependent, at any rate in the main, on tissue changes associated with an enhanced osmotic tension. Endothelial vacuolation, fluid imbibition of the connective tissue and the muscular fibres, are all to be attributed to the same common factor. Here again these changes are accompanied with blood extravasation round the vessels, which is especially marked in the vicinity of the foetal structures.

We are thus enabled to affirm, in so far as our investigations justify a general statement of the facts, that in the production of oedema the part played by purely mechanical influences, in the shape of an increase in intravascular pressure, falls into insignificance beside that enacted by tissue changes. The fluid escape would seem to correspond not to a passage from vessel to tissue in the direction of least mechanical resistance, but rather to a diffusion in the direction of greatest osmotic tension. It remains to be seen whether or not the same law applies to the physiological escape of fluid from vessel to tissue, which constitutes lymph-formation.

It will have been noted that the histological changes of the tissues, which are recorded in the foregoing pages, have permitted of a determination of the mode of escape, at any rate, in the initial stages, of the watery element of the blood only. How far this is associated in these stages with a transference of the saline and albuminous elements we are unable to state with any degree of certainty.

If our interpretation of the menstrual process be correct the changes which are induced in the endometrium are similar to those which are present in the tubal and uterine wall, and which are clearly dependent on the activity of the foetal elements. Is it/

it possible that during menstruation we are dealing with changes which are dependent on an activity of a similar nature? Recent research would seem to have definitely demonstrated the existence of an ovarian influence in connection with the mucosa changes. If, as Fraenkel declares, this influence originates in the cells of the Graafian Follicle, we would have a certain confirmation of the speculation just advanced.

SECTION VII.

NATURE of CHORIONIC INFLUENCE and MODE of its SPREAD.

THE NATURE OF THE CHORIONIC INFLUENCE
AND THE MODE OF ITS SPREAD.

The observations recorded in the preceding pages have demonstrated beyond doubt that the degenerative and other changes in the maternal tissues which the foetal cells induce must be dependent on some substance liberated by them. The fact that the changes are identical in all the three conditions studied, and that in the case of chorionepithelioma only the epithelial layers of the chorionic ectoderm are present, proves that this material is derived not from the foetus or the mesenchyme of the villi but from their cellular coverings.

What is the exact nature of this substance? The mode of its spread, to which I shall refer immediately, would seem to indicate that it is carried from the foetal cells in solution, and that it therefore is probably of a chemical nature. Whilst its existence has been definitely recognised by many observers it is only comparatively recently that the subject has attracted the attention which its importance merits. It has for long been surmised that many of the secrets associated with the toxic complications of pregnancy (hyperemesis, eclampsia etc.) are bound up with the chemical substances produced by the/

the chorionic cells. Hence the amount of laboratory research which the subject has called forth. Whilst in many respects there is a good deal of discrepancy in the results of the different investigators on one point there is an apparent unanimity, namely that the placental structures are exceedingly complex in their chemical constitution, and that from them a number of ferments can be obtained in vitro. Bergell and ⁽¹⁾Liepmann in 1905 demonstrated the existence of ferments acting on carbohydrates (diastase, lactase, and a glycolytic substance) and on proteins. The presence of a proteolytic ferment was denied by Charrin ⁽²⁾ and Goupil in 1906. ⁽¹³⁾Savare in 1907, after freeing the placenta from blood, which contains active ferments, was able to detect both proteolytic and amylolytic ferments, in addition to several others.

While it must be admitted that the subject still awaits further and more convincing elucidation it is suggestive, especially in view of the investigations I have recorded, to find several of the observers describing the existence of enzymes that have a distinct dissolving action. In all the three sites of foetal invasion studied in the preceding pages I have pointed out the indisputable occurrence of some influence/

influence which arises in the chorion and which tends to throw the maternal tissues into a state of solution. This tissue change was most evident in the muscular elements, which invariably, in the neighbourhood of the foetal cells, break up and disappear. Whilst most marked in the immediate proximity of the chorionic elements, the change is often evident at a long distance, a fact which proves conclusively that the crumbling away and ultimate disappearance is not due to a phagocytic action. The same dissolving activity of the chorionic cells on the maternal tissues has been described by Bryce and Teacher in the case of their ovum implanted in the uterine mucosa. In the account of their very early specimen they especially refer to the absence of any phagocytosis and they advance the belief that the changes are probably dependent on some extracellular substance, perhaps on enzyme, liberated by the foetal cells.

Laboratory research has demonstrated that the products of protein digestion have an osmotic tension greater than that of the substance from which they are derived and it seems to me that in this fact we must look for an explanation of the phenomena, which I have described on the preceding pages. In the degenerating muscle I have shown there are undoubted/

undoubted evidences of an increased osmotic pressure with an attraction for fluid. Here the disintegrative process culminates in a solution of the muscular substance, in other words there is a true digestion. This change is dependent on the especial susceptibility of this tissue to the chorionic influence. In the case of the endothelial and connective tissue elements, on the other hand, the resistance offered is greater and, for the most part, the protoplasmic changes do not advance beyond a splitting-up of the cytoplasm with an active osmotic imbibition of fluid by the cell, the nucleus of which usually retains its vitality throughout. Whilst this cellular change is widespread and, in all the conditions described, results in an extensive passage of fluid and blood into the tissues, it does not necessarily produce a dissolution of the cell. This is rare except where the endothelial or connective tissue elements are strangled in the disintegrating muscle. I have pointed out that in the pregnant tube there is conclusive evidence of the fact that the protoplasmic alterations in the endothelial and connective tissue cells lead in many cases to a more regular escape of the blood along newly formed tracks created by the confluence of the fluid spaces in the cells, /

cells, in other words that the process induced by the chorionic influence is, in these cases, no more degenerative in nature than is the formation of new blood vessels. The explanation of the new formation is identical with that which accounts for the gradual dragging of the intravascular contents into more and more distant parts of the tubal wall but in a more irregular manner.

With regard to the mode of spread of the chorionic secretion the investigations recorded in the preceding pages furnish evidence of considerable importance. In the first place, the maternal changes are invariably most marked in the immediate proximity of the foetal elements, and become less and less marked as the immediate site of their activity is left. The degree of involvement of the maternal structures is, for the most part, inversely proportional to the distance from the foetal cells. This observation would seem to indicate that the biochemical influence extends its action by a process of diffusion. The effects of this diffusion are often marked at a long distance from the actual embryonic site. The only exception to this law is that the walls/

walls of the veins and the tissues adjoining them are often more involved in the degenerative process than the arterial walls and the tissues immediately surrounding them. These facts indicate, what we would expect, that the chorionic substance is disseminated in a manner different from that just mentioned. In this case there has occurred a transference along the vessels in the direction of the blood flow.

CHANGES IN UTERUS IN NORMAL PREGNANCY.

CHANGES/

SECTION VIII.

CHANGES in UTERUS in NORMAL PREGNANCY.

CHANGES IN UTERUS IN NORMAL PREGNANCY.

It will be recalled that one of the main objects which I set before me in conducting the investigations recorded in the preceding pages was to determine, if possible, the exact manner in which the growing embryo is furnished with its supply of maternal blood, and especially to discover the relationship existing between the mode of operation of this process and the structural character of the stroma and vessels of the uterine mucous membrane to which I have referred in the first sections of this research.

I have shown that the main characteristic of the vessels of the endometrium is that, by virtue of their peculiar structure, they are adapted, in a manner which must be considered to be perfect from the point of view of efficiency, to open up and discharge their contents into the adjoining part of the stroma. Almost immediately after reaching the endometrium the vessels, which extend from the muscular wall of the uterus, throw off their specialised supporting coats. Except in the very deepest region of the mucosa, the walls of the vessels are completely devoid of elastic and muscular tissue, and are formed /

formed by the surrounding connective tissue elements. Where necessary these are packed together to lend support to the vascular wall, but in such a way as to permit of their ready separation when the occasion should arise. If my conclusions were correct the internal layer, also, is formed by cells which coincide in every respect, with the stroma elements. As the result of the study of the vascular changes during menstruation, I have shown that, by a detachment and separation from one another, not only of the more external cells but also of the lining cells, there is allowed an immediate and free escape into the surrounding stroma of the contained fluid and corpuscles. In the ease with which these changes occur the consistence of the stroma plays an important part. We have seen that during menstruation the stroma must be considered to consist of a soft, semi-fluid material. This determines at once the facility with which the vascular walls become teased out and the ease with which the liberated contents can pass into and displace the surrounding stroma. In this way only can we understand how there is created, especially round the glands and under the surface epithelium, the large fluid and blood areas which appear in the menstrual mucosa.

We may be sure that these peculiarities in the structural character of the mucosa vessels and stroma are, in some way or other, bound up with the changes which the ovum induces in its proximity after coming into contact with the maternal tissues. For a perfectly convincing demonstration of the exact nature of these changes I would, of course, require a specimen of the mucosa in which a young ovum had just become engrafted. If, as I am convinced, in the case of a normal pregnancy, the true nature of the tissue reaction to the growing ovum is obscured as soon as a definite decidual formation occurs, it is clear that for a satisfactory investigation we must have recourse to a very early embryo. The reasons for this belief I shall state in the course of this discussion. Suffice it for the present to recall the well-known fact that, after the development of the decidual membrane, the embryonic structures lie, for the most part, floating free, in a cavity bounded by a homogeneous cellular mass. Through this course the uterine vessels which open out directly into the gestation cavity, and, at their gaping terminations, leave little or no trace of the manner in which this result has been accomplished. In the decidual vessels, however, as I shall subsequently point out, we may glean some evidence of a circumstantial nature in connection with our enquiry as to the /

the actual manner in which the foetus is provided with its blood supply.

For want of a sufficiently early specimen (and the great difficulty associated with the procuring of such is demonstrated by the fact that the two earliest human embryos yet described are probably as old as 13 or 14 days - Peters and Bryce-Teacher) , I have endeavoured to elucidate the process in operation in the first place by endeavouring to discover the real nature of the uterine stroma, and, during menstruation, the functional changes which this subserves, and in the next place, by obtaining as accurate evidence as possible regarding the mode of action of the chorionic epithelium. For the latter purpose I have preferred to study the changes which the foetal elements induce in the tubal wall and in the uterus in the conditions described above, rather than in the uterine mucosa of pregnant animals. In explanation of this preference I would advance the well-recognised fact, that investigations conducted on animals have, because of the great difference between the structural changes found in them and in the human, so far yielded results which are not only conflicting in their nature but eminently unsatisfactory in their application to /

to the human uterus. It seemed to me more than likely that, being compelled to reason by analogy, we would obtain as good, if not more reliable, information by a study of the pregnant tube.

MODE OF FORMATION OF OVUM BED, ESPECIALLY
WITH REGARD TO THE MANNER IN WHICH THE MATERNAL
VESSELS OPEN UP.

SITE OF OVUM BED.

After reaching the uterine cavity the fertilised ovum passes, by some process, the nature of which we still imperfectly understand, into the subepithelial tissue. By some it is supposed to burrow through the smooth surface of the endometrium (Peters, Graf. v. Spee, Leopold, etc.). By some it settles in a small depression on the mucosa surface (Bryce-Teacher), or in a crypt between two folds, such as described in the case of the Hedgehog by Hubrecht. To reach the subepithelial tissue it is clear it must destroy the superficial epithelium. The degree of this destruction is probably small. Whether it is due to a phagocytic or to a corroding and dissolving action we are not certain, though in view of the markedly softening influence which the chorionic elements exert on the maternal tissues, it is not unlikely that the superficial destruction is accomplished by the latter process. This is especially probable from the fact that, in addition, the existence of a phagocytic activity has not been demonstrated in the /

the cells of the human foetal ectoderm.

After reaching the uterine stroma it forms for itself a nest consisting of a hollowed out region of the mucosa, where it is in intimate relation to the maternal blood, from which it abstracts its nourishment. In this place we are especially concerned with the mode in which the cavity in the mucosa is formed and the manner in which the maternal vessels open up to provide the growing ovum with its food. It seems to me that the investigations which I have recorded in the preceding pages provide us with a clue to the explanation of many of the changes present. In many instances, in their results the alterations produced in the maternal mucosa by the engrafted ovum coincide accurately with those which we have noted in the abnormal regions of chorionic activity. In the normal site many of these results are still imperfectly understood and it seems not unlikely that in their production influences similar to those noted above have been in operation. As we have hitherto been dealing with conditions abnormal in their nature it will be necessary to exercise considerable caution in attempting to apply information thus obtained to the normal. In the ensuing pages I intend to limit my remarks to the discussion of these changes which are similar in both cases and which, so far, have eluded a satisfactory explanation.

For a study of the early changes which the maternal tissues exhibit in response to the presence of the ovum we are provided with three young specimens - those of Peters, Bryce and Teacher, and Leopold.

PETERS' OVUM. (1899). (Plate XVIII)

In this, we have, thanks to the scientific precision of the descriptions and the excellent accompanying plates, an opportunity of studying the maternal changes, which, I believe, represent the earliest phase of the process. The reasons for this belief I shall advance in connection with the summary of the changes exhibited by the Bryce-Teacher specimen.

The ovum lies imbedded in the mucosa immediately under the surface epithelium, several of the cells of which have disappeared. At its outermost pole it is separated from the uterine cavity only by a cap of blood clot.

THE OVUM. This is a lenticular mass. It measures 2.4×1.8 mm. in its external diameters. The longest diameter is parallel to the surface of the mucosa. The surface of the blastocyst is formed of ordinary trophoblastic cells (Langhans') several layers deep. At some regions, especially towards the basal /

the basal aspect, the cellular layer is thicker than at others. The trophoblast is not solid, but is broken up by a large number of spaces, some of which appear empty, whilst others are occupied by maternal blood. These lacunae permeate the trophoblast in a very intricate manner. Some of the cells are vacuolated. The surface of the trophoblast, and, for the most part, the walls of the lacunar spaces, are lined with a plasmodial nucleated material. This corresponds to the syncytium. By Peters this is supposed to be due to a fusion of the Langhans' cells, partly under the influence of the blood pressure, and partly by the action of the blood plasma. He thinks, also, that degenerated red corpuscles may enter into its formation. In most places the syncytial layer is poorly developed, and certainly is not so evident as is described in later periods of pregnancy. In many places it is vacuolated. The spaces thus produced may be occupied with maternal blood. The embryo is situated at the basal aspect of the blastocyst cavity.

THE MATERNAL TISSUES. The surrounding maternal tissues are markedly cedematous and are infiltrated with red blood corpuscles. The cedematous condition Peters attributes partly to the intense vascular congestion and partly to an accumulation of the assimilation products which pass between mother and /

and child. In places it has led to a wide separation of the stroma cells and they are then seen to be united with one another by long filamentous protoplasmic processes. Many of the stroma elements, especially in the proximity of the ovum, are enlarged to form decidual cells. This change has recurred only to a comparatively small extent. It is much less evident than in the Bryce-Teacher ovum and in later periods of pregnancy. Throughout the maternal tissues the cedematous spaces separating the decidual cells are occupied with red blood cells. The irregular nature of the fluid and blood escape into the tissues is one of the most remarkable features of the Peters ovum. It is most marked round the ovum, but it is evident even at a distance from the embryonic structures. These changes have led to an increase in the thickness of the mucosa in the proximity of the ovum.

The vascular changes are for us especially important. In the area of the mucosa just beyond the site of the ovum there are evident large numbers of small vessels. Arteries with their ordinary supporting coats are seen pursuing their way towards the epithelial surface, often in a cork-screw like fashion in the partition between the gland spaces, which /

which are dilated in the deeper part to form a spongi-
 osa. In the immediate proximity of the embryo the
outer supporting cells of the vessels became detach-
 ed and they are often seen to be lined by a single
 layer of endothelial cells. That this condition
 has affected the arteries is proved by the fact that
 in this region there is no evidence of the comparat-
 ively thick walls which we associate with them. In
 some places at a greater distance from the ovum we
 can see the process of detachment in action - at one
 part of its course the same artery may exhibit the
 ordinary concentric arrangement of the supporting
 cells & at other regions on either side of this we
 see it denuded of these outer cells and represented
 only by an endothelial layer.

The most remarkable change in the vessels
 is the increase in their diameters. In the proximity
of the ovum this has occurred in places to an enor-
mous degree. On the serotinal aspect of the ovum
 there is a large blood tract which, on its lower
 aspect and laterally, has deeply invaded the surround-
 ing tissues (Plate XVIII). It is lined, for the
most part, by a layer of flattened cells. These
 are absent in some parts. Through its wall it is
 often possible to recognise the blood cells streaming
 into the surrounding tissues. From this large blood
 lacuna there are a row of smaller blood spaces ex-
 tending /

extending round the base of the ovum in a curvilinear manner, like the meridians of a globe. Here and there they open into the lacunar spaces on the chorionic surface.

In the proximity of the ovum the blood spaces have, as the result of their expansion come right up against the chorionic surface, and are separated from this only by an endothelial layer. In many places this is lost and the vascular contents thus bathe the chorionic surface directly. (Figures 151-152). In this region there is evidence of rupture of the endothelial layer with a liberation of the blood into the embryonic lacunae. Peters thinks that this is due to the intravascular pressure, predisposed to by a thinning out of the vessel wall, and a degenerative softening change in the endothelial remnants. Extending across the spaces intervening between the expanding vessels and the chorionic surface there has been in many places an escape of the fluid and corpuscular elements of the blood. (Figure 152.).

As I shall immediately indicate, there are, in respect of the above vascular changes, (those underlined) striking resemblances between them and those which we have detected in the pregnant tube and in the chorion-epitheliomatous uterus. The striking similarity between the response of the maternal tissues in these differing conditions is still further /

further emphasised by the discovery in Peters specimen of another vascular change which we have already recognised in the above abnormal sites of the foetal elements. This is found in the shape of a formation of new capillary vessels round the periphery of the ovum. According to Peters, in the mucosa round the trophoblast, the new vessels have apparently been formed chiefly by a projection of buds from the original vessel walls. These become canalised and occupied with blood. These newly built capillaries, at first quite narrow, widen and come into contact with the trophoblastic buds as they grow into the spaces of the oedematous stroma. (Figure 154.). Peters states that this new vessel formation can have only one object, namely that of carrying blood to the peripheral layers of the trophoblast.

The BRYCE-TEACHER OVUM. (1908) (Figures 155-156).

THE OVUM. In its external diameters this measures $1.95 \times .95$ 1.10 mm. It lies in a cavity of the mucosa just under the surface epithelium. This has been detached. At its outer pole there is a small dimple, probably corresponding to the site of entrance. There is no fibrin cap such as is present in /

in Peters' ovum. The blastocyst wall is composed of a uniform layer of trophoblastic cells, and, external to this, by a large and irregular meshwork formed by plasmodial strands. This, in places at its outer part, lies up against the walls of the gestation cavity. The meshes are formed by spaces of varying size in the plasmodium. The larger spaces are towards its outer aspect. Some are apparently empty, whilst others are occupied by maternal blood. According to Bryce and Teacher, these spaces are, to begin with, probably formed by the accumulation of digestive juices which escape and allow of the entrance of the maternal blood. It will be noted that the syncytial development is, in this specimen, much more evident than in Peters' case. The embryonic rudiment is considerably distorted and occupies a central space formed by a shrinkage in the mesoblast.

THE MATERNAL TISSUES. The ovum lies in a cavity formed in the superficial part of the mucosa, which is thickened and projects somewhat into the uterine cavity as a "decidual lobule." The walls of the implantation cavity are, for the most part, smooth all round. There is, in this respect, a marked difference between the present specimen and that of Peters, where the confines of the embryonic chamber/

chamber were extremely irregular in nature and in many places straggled into the adjoining tissues. There is a well-marked decidual formation round the embryonic cavity. In many places this has resulted in the production of large areas composed of large densely packed cells such as are found in the decidual membrane of a later date. The surface of the decidual tissue immediately opposed to the implantation cavity is markedly necrosed. It is represented by "hyaline, darkly-staining, and nearly nuclear-free zone". This appearance, as we have seen, is completely absent in Peters' Specimen. The blood-vessels of the decidua are greatly dilated, and in many places, especially under the blastocyst, there has occurred extensive haemorrhages. In one part of the sections (the upper in the plate) the necrotic zone of the decidua is broken up by a haemorrhage. On the basal aspect of the decidua the dilated vessels have formed the "blood cushion" similar to that seen in the case of Peters' specimen, and also in an early ovum described by Graf v. Spee, whilst there is marked haemorrhage throughout the adjacent maternal tissues it is/

is not present to nearly the same degree as is exhibited by Peters' ovum. There is not the same widespread infiltration of the immediately adjacent tissues with blood, and the blood vessels, though expanded, are in the immediate vicinity of the gestation cavity often seen to possess well defined walls. (Figure 155).

DOES THE BRYCE-TEACHER OVUM REPRESENT AN EARLIER
PHASE THAN THAT OF PETERS?

In the description of their specimen, the writers maintain that it corresponds to an earlier stage of the imbedding process than that of Peters. As the correctness or incorrectness of this claim is of considerable importance from the point of view of the present endeavour to throw light on the changes involved, I propose to discuss the matter in some detail.

(1). In the first place the decidual reaction in the case of their specimen is much more marked than in that of Peters. In the latter it is present to a degree less evident than in any other specimen described, whilst in the former it is seen in a manner closely suggesting the structure of the ordinary decidual /

decidual membrane of a later date. If Peters' specimen be normal, and I understand the two authors are not prepared to question its reliability, (Teacher has expressed himself clearly on this matter,) it is clear that from this point of view their specimen would seem to correspond to a later phase of the process.

(2.) In Peters' specimen there is little evidence of a necrotic change in the surrounding tissues, and certainly not to the degree present in that of Bryce and Teacher. As is well known, in the later stages of placentation the surface of the decidual membrane bordering on the intervillous space exhibits a distinct necrotic change. From this point of view, also, the Bryce-Teacher ovum corresponds to a later phase.

(3) The surface of the implantation cavity in the Bryce-Teacher specimen is, on the whole, smooth and regular, in this way coinciding with the appearances seen at a later date. In the Peters' ovum, on the other hand, the cavity is markedly irregular in nature, and thus differs from other described specimens. If it be normal, and we have no reason to doubt this, it must correspond to an earlier stage /

stage of the process of imbedding.

(4.) The maternal tissues in the Peters' specimen are markedly spread apart by an oedematous and blood infiltrate, and to a degree greater than in that of Bryce and Teacher, which, here again, corresponds to the recognised condition found in the later placenta.

(5.) THE OVUM IN THE TWO SPECIMENS.

The external measurements of the Bryce-Teacher ovum, it will be seen, are smaller in every direction than those of Peters' specimen, and from this point of view it seems, at first sight, justifiable to consider that we have distinct evidence in support of the claim the authors advance in favour of its representing an earlier phase of the imbedding process. Against this, however, may, I think, be urged the well-known fact that the size of a foetus or of a gestation cavity is not necessarily a criterion of the age. In later periods of pregnancy two foetuses of the same age may differ within wide limits as far as measurements are concerned, and also in the degree of uterine distension which they induce. How far this discrepancy in size is found in the earlier days of foetal development, it is still impossible to /

to say, but it would seem not unlikely that it does exist. In any case the arguments which I have advanced above prove beyond doubt that in many of the maternal changes which have been caused by the engrafted ovum we must recognise in the Peter's specimen an earlier phase of the process.

THE PLASMODIAL LAYER.

I have referred to the fact that in Peters' specimen this is, on the whole, more poorly developed than in the later periods of pregnancy. On the other hand, in the Bryce-Teacher ovum it is present to a remarkable degree and exhibits a structural character so far unrecognised in the human ovum. If both the specimens are normal and the claim advanced by Bryce and Teacher be correct, it is obvious that in the development of the human ovum the plasmodial layer, in the earlier stages constituting a comparatively large amount of the substance of the wall of the blastocyst, in the course of a few days thins out to a mere shadow of its original condition and then again increases in amount. This, I maintain, seems unlikely and until we are provided /

provided with information of the occurrence of such a series of changes, we are entitled to assume that the highly developed syncytial layer of the Bryce-Teacher ovum represents a later stage of development than that found in Peters' specimen. In this connection it is interesting to note that the existence of a spun-out arrangement of the plasmodial layer similar to that present in the Bryce-Teacher specimen is found in an early ovum, described⁽⁶⁾ by Stolper. This specimen was larger and apparently older than either the Peters' or Bryce-Teacher ovum. As the plasmodial arrangement was present on only one aspect of the ovum, it seems, however, not impossible that it, in reality, represents a stage intermediate between the two.

In connection with this argument I may state that I have encountered the same highly developed condition and the same intricate structural arrangement of the syncytium in the course of my investigations in the pregnant tube. On such a question, I admit, it is unwise to dogmatise on the strength of an analogy drawn from an abnormal state, but it /

it is, at any rate, suggestive to find that the condition is present only in the case of the tubes, the seat of a well-advanced pregnancy. (Figure 157).

THE EMBRYO.

In the Bryce-Teacher ovum the embryo is considerably distorted and somewhat broken-up. In spite of this a careful examination of the component parts has enabled the two observers to recognise in it an earlier phase of the human embryo than that present in Peters' ovum.

If their interpretation of the conditions present be right, we are thus compelled to admit that in the Bryce-Teacher specimen we have an ovum in which, whilst the embryonic rudiment corresponds to the earliest phase yet described, the maternal tissue changes correspond rather to a later stage than the Peters' specimen.

LEOPOLD'S OVUM. (1906).

This corresponds closely to Peters' specimen, in the mode of attachment of the ovum to the uterine mucosa. Here there is again well marked vascular distension and haemorrhagic infiltration. That /

That it corresponds to a stage later than that of Peters would seem to be justified by the existence, in the marginal lamina of the decidua, of a well-marked coagulation necrosis. There is not to the same extent the blood and fluid infiltration of the tissues nor the formation of new vessels.

In all the other specimens of early ova the maternal changes coincide either with those exhibited by Peters' ovum or those seen in the Bryce-Teacher ovum, and it is unnecessary to relate them in detail.

APPLICATION OF THE PREVIOUSLY RECORDED INVESTIGATIONS INTO THE STRUCTURE OF THE ENDOMETRIUM AND THE MODE OF ACTION OF THE CHORIONIC EPITHELIUM TO THE CASE OF THE NORMAL OVUM.

We have seen from the earliest described ova, and more especially from that of Peters, that in response to the activity of the chorionic structures there occur the following maternal changes:-

- (1.) In the mucous membrane surrounding the implantation cavity there are found marked vascular changes. These are most evident in the region immediately adjoining the foetal structures but they are present, sometimes to a marked degree, beyond the actual site of the /

the cellular invasion. The cells forming the vascular walls become teased apart and the concentric layers of supporting cells found in the vessels of the resting state become stripped off from the lining layer. This has resulted, in Peters' specimen, in a complete disappearance of the thicker-walled vessels in the mucosa near the ovum. There is also apt to be a detachment of the endothelial cells and an opening out of the vessel wall.

(2) These changes are associated with a marked oedematous infiltration and a haemorrhagic escape into the stroma, the cells of which, except where they are packed together as the result of a decidual change, are spread apart and completely detached save for the presence of intervening branching processes of their protoplasm. Through the vessel walls the red blood corpuscles are often seen streaming into the adjacent tissues and towards the surface of the chorionic membrane. Where there has occurred a marked decidual change in the stroma elements, the watery and corpuscular infiltration of the tissues /

tissues is less marked, and the vessels, even in the immediate vicinity of the implantation cavity are apparently well supported by the enlarged decidual cells (Bryce-Teacher ovum - figure 155). In these cases the vessels can be seen pouring their blood into the gestation cavity.

(3). There is, besides a loosening of the vessel walls and an oedematous and corpuscular escape into the tissues, a marked distension of the vessels throughout the mucosa adjoining the site of the ovum. This is present in all the early specimens and is one of the most characteristic features seen. In Peters' specimen the distension of the vessels is associated with a recession of their walls towards the chorionic surface carrying in this way the contained blood to the region of the ovum. In many cases the expanding lumen is separated from the foetal surface only by the endothelial layer. In some cases, however, this may disappear. Round the walls of the expanding vessels there is a haemorrhagic escape.

The distension of the vessels results in the formation, throughout the mucosa adjoining /

adjoining the embryonic site, of large blood sinuses or lacunae. These may be lined by a layer of flattened cells or they may, in parts, be bounded apparently by the ordinary stroma cells.

(4) In Peters' specimen, in which there is less evidence of a necrotic change in the neighbouring structure than in any of the other early ova and which, in this respect, would seem to furnish us with the earliest phase of the maternal reaction, there has occurred in the decidual tissue round the ovum a formation of New Capillary Vessels.

(5) The stroma elements in all the specimens are enlarged to form decidual cells. This process is less evident in Peters' case than in that of Bryce and Teacher.

The fact that there is in both of these specimens an opening up of the maternal vessels and an escape of the contents into the surrounding tissues beyond the regions of the actual chorionic invasion would seem without doubt to demonstrate that there is in operation in the production of the haemorrhage something more than a direct invasion of the vessel walls and a mechanical liberation of the contained blood. The conditions present in /

in Peters' specimen warrant such a conclusion and in the description of their case Bryce & Teacher state that the appearances "suggest that the process of destruction is not one of erosion by direct cellular activity or phagocytosis, but a sort of digestion or solution due to the action of extra-cellular substances probably of the nature of enzymes".

It will be seen from the above resumé of the conditions present in the case of the earliest described ova that the maternal changes coincide, in so far as the vascular alterations are concerned, almost exactly with those which I have recorded in connection with the pregnant tube and the chorion-epitheliomatous uterus. We have seen how in both cases there is a well-marked oedematous and blood infiltration of the tissues, which, though most evident in the immediate vicinity of the foetal elements, is, as in the early ova just described, still manifest at a distance from the actual site of the cellular invasion. We have seen also, a marked vascular distension in both regions, which especially affects the vessels with thin walls, and we have, in addition, observed how, in advance of the chorionic line of attack, the vascular walls became opened out and the vessel virtually advances through the tissues towards the chorionic surface.

In all these respects

respects, then, the phenomena are similar, be it in the uterine mucosa in a normal pregnancy, in the wall of the pregnant tube, or in the endometrium or muscular wall of the uterus in the case of chorion epithelioma. In all these conditions the resulting maternal changes are determined in response to the same influence which, as we have seen, is in all probability to be identified with an enzyme or enzymes liberated by the chorionic cells.

How does the chorionic influence act in the case of the normally engrafted ovum? We have seen that a direct cellular invasion and erosion fails completely to account for all the changes exhibited by the maternal mucosa in the neighbourhood of the Peters' and Bryce-Teacher embryos. What other influence must be invoked? It seems to me that the investigations recorded in the preceding pages endow us with a means of indicating the probable nature of the changes in a more efficient manner than any previous explanation. Before discussing this, however, we must review in brief the respects in which the maternal tissues in the sites of the abnormal foetal activity, which we have studied, differ from the mucosa of the uterus in their behaviour to the chorionic influence. We have seen how throughout /

throughout the wall of the pregnant tube and the uterine tissues in chorion-epithelioma and in the case of retention of placental fragments there has occurred a marked and extensive disintegrative change. Such a change is almost completely absent in Peters' ovum and in the Bryce -Teacher specimen. As in all the later stages of placentation, it is almost entirely limited to the decidual tissue immediately opposed to the implantation cavity. The rationale of this marked difference in the two sets of conditions is easily understood when we remember that in the pregnant tube and in the uterine wall in the other cases, the necrotic change is due mainly to the fact that the muscular tissue has exhibited a special susceptibility to the bio-chemical influence of the chorion. It early undergoes a degenerative and softening change and ultimately becomes replaced by a homogeneous structureless and necrotic mass, which, in the immediate vicinity of the foetal cells, disappears, apparently entering into a state of solution.

In contra-distinction to this progressive degeneration of the muscular tissue it was found that the connective tissue elements throughout the corresponding regions have resisted the destroying agent and, even in the immediate vicinity of the chorionic line of attack, have retained their vitality as seen in /

in the presence of well-preserved nuclei. It is more especially in the changes which these latter cells exhibit that we are provided with a probable explanation of the manner in which the uterine stroma reacts to the engrafted ovum.

I have shown in the course of the investigations previously recorded that the changes, which result in a teasing asunder of the vessel walls and, in some cases, in a marked expansion of their cavity, and which, in the proximity of the ovum, culminate in a wholesale escape of their contents, fluid and corpuscular, are all dependent on tissue changes, which lead to an active fluid imbibition. These changes are associated with protoplasmic alterations set in action by the chorionic influence, which result in an increase in osmotic tension, probably due to a liberation of crystalloidal elements. This condition was distinctly visible in the endothelial and the connective tissue cells. Throughout the affected regions these cells were seen to have actively imbibed fluid, which, in many instances, could be traced back to the neighbouring vessel. The dropsical escape thus established we have seen led to an opening-out of the supporting elements of the vessel wall and, in many cases, was succeeded by an exodus /

exodus of the red cells into the surrounding tissues especially in the proximity of the chorionic cells. In no cases was it possible to detect that the liberation of the blood constituents was due to a direct cellular erosion of the vessel wall with a subsequent mechanical escape. The same tissue changes I have shown to be responsible for the gradual expansion of the vessel walls. In some cases this consisted in an irregular invasion of the surrounding tissues by the distending vessel. This condition was associated with a disappearance by solution of the neighbouring tissues, especially the muscular elements. In other instances, and this was especially the case in the fine walled vessels, the distension was due to the same tissue changes but differed from the latter process in the fact that the vascular expansion was more regular in nature. In these cases the distending vessel wall was seen to incorporate as an endothelial layer the connective tissue cells which were encountered in the process of expansion. We have seen, moreover, and in the wall of the pregnant tube it was often exhibited with a diagrammatic clearness, that the same osmotic changes in the tissues determined the new capillary sprouting from the pre-existing vessel walls. In this process, also, /

also, the adjoining connective tissue cells took a share in the formation of the new endothelium.

I have indicated that, to account for all the changes present in these abnormal locations, it was necessary to assume a similar activity, in the shape of an imbibition of the fluid element of the blood, in the case of the degenerating muscular elements also. This assumption was substantiated by the detection in the muscular fibres of the same process in action. The presence of the muscular tissue, then, besides explaining the wide-spread necrotic changes which were found in these abnormal sites of chorionic activity, introduces an element of difference between the mode of tissue reaction in these regions and in the stroma of the uterine mucosa which consists throughout of a connective tissue structure. The explanation of the other well-marked difference, namely the uncontrolled oedema and haemorrhage which occurs in the pregnant tube and the uterine wall in the conditions we have studied, I shall discuss in the next section of this research devoted to the Function of the Decidua.

EXPLANATION OF THE CHANGES IN THE UTERINE MUCOSA,
IN RESPONSE TO THE CHORIONIC ACTIVITY.

In view of the above considerations and the previously recorded investigations, I venture to claim that we are furnished with a probable explanation of the manner in which the uterine mucosa reacts to the chorionic influence.

I have pointed out in the first section of this research that, throughout practically its entire thickness, the uterine stroma is to be looked upon as consisting of a connective tissue, in which there is only a comparatively small attempt at differentiation into cellular elements. Its structural characters suggest strongly that the supporting elements of the vessel walls are constituted, except in the deepest portions of the stroma, where there is occasionally a small amount of elastic tissue present, entirely of this undifferentiated connective tissue. In discussing the histology of the endometrium, I advanced arguments which strongly suggest that the endothelial lining of the vessels, also, is composed of elements structurally identical with those of the stroma. This contention, I maintain, is supported by the discovery in other regions that, under the influence of the chorionic activity, the endothelial and the connective /

connective tissue cells exhibit identical changes, and that, under certain circumstances, the latter cells can participate in the formation of a new endothelium. Additional support is lent to this conception of the nature of the endothelial lining of the stroma vessels by the fact, which I shall refer to more particularly in the next section, that endothelial elements can undergo a decidual enlargement similar in every respect to that of connective tissue cells.

Being composed of connective tissue, then, it seems to me highly probable that, in response to the chorionic influence, the stroma will react in a manner similar to that exhibited by the connective tissue cells in the regions which we have been able to study with clearness. By such a process, i.e., one dependent on a protoplasmic change associated with a rise in osmotic tension, we can explain the vascular distension, and the oedematous and the blood escape into the surrounding tissues. In this way the provision of the necessary supply of maternal blood for the engrafted ovum would, as in the other cases, be determined by changes which enable the tissues to take an active share in the process. We have /

have seen that a mere passive destruction or erosion of the maternal tissues completely fails to explain the phenomena!

The soft, semi-fluid consistence of the uterine stroma, to which I have referred in connection with the menstrual process, now, in view of these facts, amply justifies its existence. I have shown how during menstruation this structural peculiarity of the stroma permits of an easy teasing asunder of the elements of the vessel wall and culminates in many cases, especially toward the outer aspect of the mucosa, in a wholesale expansion of the vessel and a displacement of the surrounding tissues by the liberated fluid and blood. Under these circumstances the unaltered stroma is seen to form the walls of the newly formed blood space. In the ordinary mucosa the actual process in operation is sometimes difficult to decipher, but where the vessel walls are thickened it is forced into prominence and we then discover the existence of an active, intra-cellular fluid imbibition. In another section of this research, I have advanced such a process as an explanation of the menstrual changes exhibited by the mucosa.

In /

In the case of Peters' ovum there were present alterations in the vessel walls identical with those seen during menstruation. In the proximity of the chorion there was the same stripping of the outer cells from the underlying endothelium and the same detachment of the cells forming this layer. We thus see that the structural peculiarities of the uterine mucosa subserve, and efficiently adapt the stroma for, the functional changes exhibited during pregnancy. In this observation is furnished a substantiation of the prediction which I was led to make in an earlier part of this research. These investigations, moreover, would seem to suggest that the influence operating during menstruation is similar, if not in origin, at any rate in its results, to that in action during pregnancy.

If the conclusions, to which my investigations have carried me, be correct, it would seem highly probable that the formation of the implantation cavity has occurred more by a process of tissue activity and tissue displacement than by a wholesale destruction of the stroma by the foetal cells. The excavation of the mucosa is no more or, at any rate, little more, associated with a process of disintegration en masse than is the formation of the large cavities of the blood lacunae in the mucosa, or than is the enormous distension of the venous sinuses /

sinuses in the muscular wall. The difference is merely a difference in degree, and is attributable to the semi-fluid, easily displaceable nature of the uterine stroma. I would submit that this explanation of the phenomena is substantiated in a most convincing way by the conditions present in the Peters' specimen. Here there is little tissue destruction at a time when one should, according to the orthodox conception, expect it to be in full swing. The local epithelial destruction is simply an evidence of a change which ultimately results in a widespread softening and shedding of the epithelial cells. A corollary to the interpretation I have just advanced is that the disintegrative process seen in the intervillous regions of the decidua serotina and reflexa is to be looked upon more as an incident in the process than as an indication of the mode of production of the implantation chamber. It seems to me that the conditions present in the Peters and the Bryce-Teacher specimens prove beyond doubt that the tissue necrosis, which never involves more than a comparatively small area of the serotina, sets in subsequent to the formation of the implantation cavity. This I shall again refer to in a later section.

If the chorionic influence acts in the manner which I have suggested, we should expect some evidence of such an action in the pregnant uterus at a date later than that corresponding to the early ova just described. Have we no such evidence?
As/

As I have indicated in several places the establishment of the marked decidual transformation of the cells which characterises the uterine mucosa except in the earliest days of pregnancy obscures the exact manner in which the vascular changes in the immediate proximity of the ovum are accomplished. This I shall discuss more fully on a later page. For this reason the progress of pregnancy beyond the first few days precludes the possibility of our eliciting accurate first-hand information on such a question. The existence of an influence such as I have advanced we are able, however, to confirm by a study of some of the changes in the vessels and the decidual cells in the mucosa, and the vessels of the muscular wall of the uterus at a later date of pregnancy.

CHANGES IN THE VESSEL WALLS AND CELLS

OF THE DECIDUA.

For this investigation I have been able to obtain three uteri removed from gravid women within the first half of pregnancy. In two cases, where the uterus was removed by operation for carcinoma of the cervix, the pregnancy had advanced to $2\frac{1}{2}$ months and /

and $4\frac{1}{2}$ months respectively. The other specimen, which corresponds to a pregnancy of 4 months, was removed from a woman who died from acute intestinal obstruction.

In all these specimens I have been able to discover changes in the decidual membrane of a nature similar to those detected in the wall of the pregnant tube and the uterine wall and the secondarily affected tissues of the lung in the case of chorion-epithelioma. In the normal condition, of course, there are never the same extensive oedema and blood extravasation as were found in these abnormal sites. In fact, as I shall endeavour to prove in the next section of this research, the occurrence of an uncontrolled fluid and corpuscular escape such as were encountered in these regions is prevented by the enormous enlargement of the stroma cells which takes place during pregnancy. If this be true, namely that the decidual change is intended as a protection against the occurrence of an irregular blood escape into the tissues, we would not be surprised under ordinary circumstances to find a complete absence of the endothelial and connective tissue changes which were detected in the abnormal sites of chorionic activity. In point of fact I have /

have been able, in all the specimens which I have examined, to discover evidence of the existence of tissue changes, which, though diminished in degree, are in nature exactly similar to those which I have called attention to in the preceding sections of my research.

In many of the vessels of the decidua, even at a distance from the placental site, changes similar to those depicted in figs. 158-160 are visible.

The vessels represented are from the several

decidual membranes. Here, as before, we have the existence of changes in the endothelial cells which have determined an active fluid imbibition. The fluid has accumulated in the cells under a considerable hydrostatic tension, and has led to changes similar in every respect to those noted in the abnormal regions of chorionic activity. Here and there throughout the decidual membrane the cellular elements forming the supporting layers of the vessel walls have been opened out by a fluid track extending from vessel lumen to tissue. (Figures 160-2). This condition is never well-marked. This is, in all probability, to be attributed to the fact that during pregnancy there occurs a condensation of the vascular walls. In addition to these changes associated with a dropsical collection in the vessel wall/

wall there is often present an oedematous opening out of the immediately adjoining decidual tissue. (Figure 163). To complete the picture it is often possible to detect a vacuolated condition of the decidual cells. (Figure 164). This at first sight strongly suggests the appearances associated with a fatty degeneration of the cell but that it is not due to this is proved by staining the fresh specimen with the appropriate dye. This vacuolated condition of the decidual cells would seem to have been first described by Webster.⁽⁷⁾ In his "Human Placentation" he says, referring to the normal decidua, "I have described a condition of vacuolation in nuclei or in cell matrices. The appearance is one which might easily be mistaken for fatty degeneration, but special staining reactions prove that it is not this." It is dependent on a change in the cell substance which has determined an active imbibition of fluid from the adjoining tissue space. We thus see that in the decidua changes, though less prominent in degree, are present similar in nature to those which we have associated with the existence of a dropsical escape from the vessels in other regions, and which we traced to the chorionic influence.

VASCULAR CHANGES IN THE MUSCULAR WALL
OF THE PREGNANT UTERUS.

In the muscular wall of the pregnant uterus, in addition, I have been able to detect with ease vascular changes entirely comparable to those which are induced by the chorionic influence in other regions. In the first place, in the fine-walled vessels there is the same tendency to a gradually increasing expansion of the lumen. In this way the thin-walled sinuses, which characterise the pregnant state, are formed. They vary greatly in size. In some cases they are represented by small blood spaces; in most cases, however, they attain large dimensions and may, especially after the first few weeks of pregnancy, assume the form of thin-walled sinuses extending through a large territory of the muscular wall, in the distended state transforming the uterine wall into a loose-meshed spongework. In shape, also, they exhibit similarly wide variations. In some instances, especially when small, they possess a round or oval contour. When larger, they are usually very uneven in shape, the surface irregularities corresponding to the position of the muscular /

muscular bundles. In fact it seems obvious that in the shapes assumed purely mechanical influences have played a prominent part. (Figure 165). These blood spaces are usually described as being venous in origin and they probably represent direct continuations of the venous tracks in the decidua. The great distension they exhibit is doubtless for the purpose of accomodating the excessive blood flow which characterises the pregnant condition. It would seem not unlikely that the constant intermittent contraction of the muscular wall which occurs during pregnancy must assist in maintaining the circulation through these spaces, in which, otherwise, it would almost certainly be very sluggish.

In their characteristics we at once note a complete similarity between these spaces and the distended blood tracks which form in the muscular wall of the uterus in chorion-epithelioma, and the wall of the pregnant tube, which I have demonstrated owe their origin to the tissue changes induced by the activity of the chorionic cells, & which, in all probability, are associated with the liberation of an enzyme whose function is the production of protoplasmic changes that determine an active imbibition by the cells of the blood fluid. We have seen how, especially /

especially in the case of the pregnant tube, where the process was clearly discernable, these cellular alterations led to a gradual expansion of the fine-walled vessels at the expense of the surrounding tissues, the cells of which were incorporated by the advancing wall to form a new endothelial surface. In the case of the pregnant uterus I have been able to detect cellular alterations similar in every respect to those described on a former page, but I have been unable to carry the analogy to the extent of a complete demonstration of the fact that the existence of these changes is the controlling influence in the increasing expansion of the uterine walls into the large sinuses. In spite of this fact, however, I feel that such, in all probability, is the case. In this place, also, I may state, what at first sight may seem a truism that the limit of the expansion of these uterine sinuses must, from the close manner in which they fit against the muscular bundles, be determined by the presence of the latter. An extreme and uncontrolled expansion of the walls, such as is apt to occur in pathological regions of chorionic activity, is prevented by the fact that, whereas in the latter sites there is apt to be a progressive muscular disintegration in the pregnant uterus there occurs a progressive development of the muscular fibres /

fibres, and an increase in size of the bundles.

Whilst, then, a study of the fine-walled vessels in the muscular wall furnishes us only with indirect evidence of the existence in the normal pregnant condition of an influence such as I have advanced, an investigation of the thick-walled vessels leaves little room for doubt on this matter. Throughout the uterine wall in all my specimens I have been able to discover with ease vascular changes in every respect identical to those met with in the pregnant tube and the chorion - epitheliomatous uterus.. Here again we have undoubted evidence of tissue changes leading to an active abstraction of fluid from the vessel lumen. We have the same fluid distension of the endothelial cells, the same tendency to a separation and bulging towards the lumen of the endothelial sheet, and from this region we have the same opening - out of the muscular tissue by oedematous tracks which extend into the neighbouring tissues. (Figures 166-168). We have in addition, the same evidence in the shape of an active fluid imbibition and distension of the connective tissue elements. All these changes prove beyond doubt that in the occurrence of the fluid escape there is in action some tissue alterations and/

and not a mere mechanical filtration from vessel lumen, where the fluid pressure is higher, to tissue space, where it is lower. In the uterine wall these changes are on the whole most manifest in the veins in the proximity of the placental site. This is due, in all probability, to the fact that these vessels are subjected to the chorionic influence more than the arteries because of the direction of the blood flow. If our contention be justified the bio-chemical influence is bound to reach them in greater concentration.

The oedematous escape in the case of the vessels in the muscular wall of the pregnant uterus is localised to the immediate vicinity of the vessel, in this respect differing from the conditions present in the abnormal sites of foetal activity which we have studied. This difference must be due to the better resistance offered by the tissues in the former case because of the well-marked muscular development which characterises the pregnant state.

I submit the information thus acquired by a study of the decidual membrane and the muscular wall of the pregnant uterus as providing the strongest circumstantial confirmation of the existence during ordinary pregnancy of tissue changes similar in nature to those which I have detected in the above-recorded abnormal regions of chorionic activity.

MODE OF FLUID ABSORPTION BY CHORIONIC SURFACE
AND ITS INFLUENCE ON THE MATERNAL CHANGES.

In several places throughout this research I have referred to the fact that the absorptive influence of the foetal elements probably contributes a share to the manner in which the maternal blood is brought right up against the chorionic surface.

For long it has been recognised that the nutritive material abstracted from the maternal blood for the services of the embryo must be taken up by the process of osmosis. The influence of this process finds its recognition in the modern text-books of obstetrics. In discussing the changes encountered in the pregnant tube and in the uterine wall in chorion-epithelioma, I have referred to the fact that this fluid absorption by the chorionic surface amply accounts for the massing of the red blood corpuscles, which is often seen to have occurred in the immediate vicinity of the foetal elements. As the result of the continual abstraction of fluid from the adjoining tissue we can see that there must be induced a stream of blood towards the chorion from the neighbouring vessels, whose walls have been teased out in the way I have described. The removal
by /

by the foetal elements of the watery part of this fluid stream must tend to lead to an accumulation of the red cells in quantity.

I would advance a similar mechanism to explain how the blood is drawn towards the ectodermic surface in the early ovum. In Peters' specimen, for example, there was seen to be a passage of red cells across the space intervening between the vessel lumen and the chorion. In this way we probably have in the immediate vicinity of the embryonic surface in operation a factor in addition to the active tissue changes to which I have directed attention. That the continual centrifugal stream thus produced must be not inconsiderable is suggested by the facts that the embryo is at this stage undergoing a rapid growth and that into its composition it is building up a large proportion of water. Fehling has pointed out that during the first few months of pregnancy the embryo consists almost entirely of water. At $2\frac{1}{2}$ months the proportion is 93.82 per cent of its total weight. It would seem not unlikely that a similar influence must be in action even in the absence of the foetus i.e., in chorion-epithelioma, and especially in view of the fact that the tumour cells /

cells are proliferating rapidly.

In the course of my studies it has been borne in on my mind that, in the structural characters exhibited especially by one of the chorionic cellular layers we have in evidence changes which seem to be dependent on the osmotic passage of fluid from the maternal blood to the foetal elements. This is found in the syncytial layer in the shape of the vacuolation which it characteristically exhibits. By most observers it is recognised that the spaces thus produced serve the purpose of receiving the maternal blood and thus of exposing the chorionic surface to a large quantity of the fluid from which it absorbs the necessary watery and other nutritive elements.

Whilst there is a unanimity on this subject in the literature there seems to be some difference of opinion as to the exact manner in which the spaces are formed. By Kastschenko⁽⁸⁾ the spaces were supposed in some instances to be occupied by young mesoblast. By other observers they indicate the accumulation of a digestive juice, which is shed, by a rupture of the bounding walls, into the surrounding area (Bryce-Teacher.) The fact that it is often present in the syncytial layer where there is no embryo, e.g. chorion epithelioma, proves that the material collecting in the vacuoles cannot be derived from /

from the foetus. (Figure 169). It must therefore be maternal in origin. It seems to me more than likely that it is not fluid which has been absorbed by the plasmodium, and then poured out in a modified form as a digestive juice, but that, in reality, it consists of fluid which has passed directly across in response to mere osmotic influences from the maternal blood contained in the adjacent space or spaces. This explanation is more in conformity with the well-recognised function of the chorion, namely the acquisition, in the shortest possible time and in the most perfect manner possible, of a supply of maternal fluid for the growing embryo. This is obtained by the presence of osmotic diffusion currents originated by the chemical nature of the plasmodium and which lead to a passage in quantity of the blood fluid into the syncytial spaces even before the breaking down of the walls has permitted an entrance of the red cells. In this way can we easily understand the intricate arrangement of spaces often detected in a plasmodial mass, the largest of which are usually towards the free surface. (Figures 155 & 156). In this way, also, we may explain the manner of origin of the plasmodial sheet which is often /

often seen spread over the decidual surface of the pregnant uterus or the surface of the tissues which are the seat of an abnormal chorionic invasion. The osmotic expansion of the peripheral spaces of the syncytial mass would lead to its being pressed up against the corresponding maternal surface. That the spaces produced in the plasmodium may attain large dimensions is demonstrated by a glance at the plates accompanying the description of the Bryce-Teacher ovum.

The same condition of vacuolation is not infrequently seen in the Langhans' cellular layer of the chorion. It is evident in Peters' specimen. Hubrecht has described this as a characteristic feature of the trophoblast of the Hedgehog in which it, as in Peters' case, leads to the formation of clear lacunae, which ultimately become filled with maternal blood. It would seem not improbable that in this region, as in the syncytium, we have in these appearances a visible demonstration of the osmotic passage across the chorionic surface of the maternal fluid, which serves the double purpose of carrying nutriment to the embryo, and of paving the way for the future entrance of the unaltered blood. This is accomplished by the giving way of the lacunar walls. /

walls. Such an explanation of the phenomena it seems to me is more consistent with the known facts. It does in no way conflict with the fact that the chorionic epithelium, in all probability furnishes a digestive enzyme.

SECTION II.

DEVELOPMENTAL FORMATION AND FUNCTION OF DECIDUAL MEMBRANE.

THE INTERRELATIONSHIP OF DECIDUAL FORMATION.

In this section I propose to discuss some points in connection with the decidua under two headings:-

1. The Size and Histological Characters of the decidua formed in the course of these implantations, and

SECTION IX.

2. The Function of the Decidua Membrana.

DECIDUAL FORMATION and FUNCTION of DECIDUAL MEMBRANE.

I have had the opportunity of studying the decidua in two different types of cases in the wall of the pregnant tube, namely in the non-implanted and in the implanted cases.

THE NON-IMPLANTED CASES.

1. Throughout the tube there is an increase in the intermuscular connective tissue elements in a manner similar to that which occurs in the uterine wall. This condition is, for the most part, most evident in the proximity of the fetal cells. (Plate VII, fig. 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 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2016, 2017, 2018, 2019, 2020, 2021, 2022, 2023, 2024, 2025, 2026, 2027, 2028, 2029, 2030, 2031, 2032, 2033, 2034, 2035, 2036, 2037, 2038, 2039, 2040, 2041, 2042, 2043, 2044, 2045, 2046, 2047, 2048, 2049, 2050, 2051, 2052, 2053, 2054, 2055, 2056, 2057, 2058, 2059, 2060, 2061, 2062, 2063, 2064, 2065, 2066, 2067, 2068, 2069, 2070, 2071, 2072, 2073, 2074, 2075, 2076, 2077, 2078, 2079, 2080, 2081, 2082, 2083, 2084, 2085, 2086, 2087, 2088, 2089, 2090, 2091, 2092, 2093, 2094, 2095, 2096, 2097, 2098, 2099, 2100, 2101, 2102, 2103, 2104, 2105, 2106, 2107, 2108, 2109, 2110, 2111, 2112, 2113, 2114, 2115, 2116, 2117, 2118, 2119, 2120, 2121, 2122, 2123, 2124, 2125, 2126, 2127, 2128, 2129, 2130, 2131, 2132, 2133, 2134, 2135, 2136, 2137, 2138, 2139, 2140, 2141, 2142, 2143, 2144, 2145, 2146, 2147, 2148, 2149, 2150, 2151, 2152, 2

AN INVESTIGATION INTO DECIDUAL FORMATION.

In this section I propose to discuss some points in connection with the decidua under two headings:-

- I. The Sites and Histological characters of the Decidual Changes detected in the course of these investigations, and
2. The Function of the Decidual Membrane.

DECIDUAL CHANGES IN THE PREGNANT TUBE.

I have had the opportunity of studying a decidual alteration in two different types of cells in the wall of the pregnant tube, namely in the connective tissue elements and in the endothelium.

THE CONNECTIVE TISSUE CELLS.

I. Throughout the tubal wall there is apt to be an enlargement of the intermuscular connective tissue elements in a manner similar to that which occurs in the uterine mucosa. This condition is, for the most part, most evident in the proximity of the foetal cells. (Plates VII&VIII) In this respect
my /

my specimens conform with those described by many previous workers on the subject. I have repeatedly, during the course of this record, referred to the existence of a vacuolated condition of the connective tissue cells scattered throughout the wall of the pregnant tube. This change is much more manifest than the decidua-like enlargement. The former change is not infrequently associated with an extreme enlargement of the cell body, but it is due, not to an increase in cell substance, but to an accumulation of clear fluid. That the two different changes are dependent on the same common factor is suggested by the fact that in one place the decidual alteration is present, whilst in the vicinity the fluid distension is present. Each of the two conditions is traceable in the beginning to the chorionic influence which in the one case determines an imbibition of fluid which collects in the cell, apparently unchanged, whilst in the other case it is coagulated or is built up into the cell substance. In each condition the nuclear changes are identical, namely a swelling and a deficient staining reaction.

2. The region of the tube where I have found the decidual change most marked is the connective tissue of the mucous folds. In one of the specimens (3 months) the condition is present in the folds throughout the entire extent of the tube from fimbriae/

fimbriae to divided uterine end. In the portion of the tube corresponding to the site of the gestation sac (the ampulla) the mucous rugae are, for the most part, detached. The decidual transformation of the connective tissue cells is most evident towards the free surface of the folds, which have become enormously expanded in the process. The cells exhibit a marked enlargement of the cell body, which is granular in appearance. The nucleus is also increased in size but not to the same extent as the cell body. The cells are closely packed together and are mostly rounded or polygonal in shape. A glance at Figures 94-5 will demonstrate that the resulting appearances coincide in every respect with what is encountered in the compact layer of the uterine decidua.

The perfect similarity between the decidual changes, which occur in the mucous rugae of the tube, and those existing in the mucosa of the pregnant uterus, is clearly dependent on the like nature of the tissue present in these two different sites. In both regions it is represented by a connective tissue of a low type.

In all my other specimens a decidual change /

change in the tubal mucosa to the extent found in this case is absent. That this difference is not dependent on the age of the embryo is proved by finding that, not only is the change poorly marked in the rugae of the specimens corresponding to younger pregnancies than this, but it is almost entirely absent in the oldest specimen of the series, i.e., 4 months.

From the point of view of one of the objects for which these investigations were made, namely, an attempt to discover the functions of the normal decidua, it is important to note that, with an exception to be recorded immediately, the only region of the tubal wall, which is not ploughed up by an oedematous infiltrate and in which the vascular walls are so well supported as to prevent a haemorrhage escape, and an increasing distension of their lumina is the subepithelial decidua of the mucous rugae. These changes are present to an excessive degree throughout the whole extent of the muscular wall of the entire series of pregnant tubes, and they are detected, in addition, in the mucous folds of those specimens in which the decidua enlargement of the cells is partially or wholly absent. (Figures 90, 91, 93, and Plate XII.).

3. In many of my sections there is present a decidua /

decidua-like enlargement of the cells of the vessel walls, where these are equipped with a muscular and connective tissue coat. In these cases the decidual elements often form a layer several cells deep; in some instances the decidual change has led to a bulging of the inner part of the wall into the lumen, which may be considerably narrowed in the process. The decidual layer is often seen to be external to an unaltered endothelium (Figures 99, 100 & 101.). This vascular change is often present at a considerable distance from the foetal elements. The cells are easily recognised from these of the Langhans' layer of the chorion by the smaller size of the nuclei and by the fact that in their neighbourhood, the maternal tissues are well preserved, a condition never found in the proximity of the embryonic cells.

Changes in the vessel walls similar to those just described have been previously observed by other authors (Hitschmann, ⁽⁹⁾Fellner, ⁽¹⁰⁾Kroemer, ⁽¹¹⁾Schambacher, ⁽¹²⁾Von Franqué and ⁽¹³⁾Garkisch, etc.). I refer to their occurrence in my specimens only for the purpose of describing their importance from an aspect which has hitherto escaped notice, namely that, whereas even in thick-walled vessels, in which these alterations are absent, there is apt to be a wholesale /

wholesale ploughing up of the walls by a fluid and blood exudation, in these cases this process is resisted, in some instances in a manner which is perfect(c.f. Figures 99,100, & 101).

DECIDUAL CHANGES IN THE ENDOTHELIUM.

In my specimens of the pregnant tube decidual changes in the endothelial cells are present in two different sites - in the vessel-lining and in the peritoneum.

DECIDUAL CHANGES IN THE VESSEL ENDOTHELIUM.

In all my specimens there are found marked changes in the vascular endothelium. The most manifest is a vacuolation of the cell body. The structural alterations associated with this, and its importance, I have already referred to in a preceding section. Another endothelial change, which has been described by a few observers, I have also noted, namely a proliferation of the nuclei and an increase in cell substance associated with the disappearance of the cellular outlines, with the production of a syncytium-like mass. In Figure 102 and 103 such a change is seen in a small vessel, situated in a portion of the tubal wall remote from the site of the ovum. That it is not due to a portion of /

of syncytium deported from the foetal area is proved by tracing the vessel in series. In the figures two successive sections of the vessel are seen, and it is observed that the lumen is empty. It looks as if the endothelial proliferation had led to the creation of the bulbous swelling in the capillary at that part.

In other regions of the affected tubes I have noted, in addition to a proliferative change, an enlargement of the cell bodies, in some cases occurring to the extent of identifying the cells with those found in the uterine decidua. In figure 104 is shown a vessel thus affected. Attached to the inner wall and sprouting into the vessel lumen is seen a mass of large cells, some of which are detached. This appearance I had several times noted in my specimens and had thought to be due to an extension along the vessel lumen of foetal cells, which were in the process of invading the vessel wall. A subsequent study of the specimens has, however, convinced me that they, in reality, correspond to enlarged and proliferated endothelial cells. In the first place they are present often at a considerable distance from the ovum. In the second place it will be noted that there is no invasion of the vessel wall./

wall. The cells can be seen springing from the endothelial layer. In the third place, they differ widely in structure from the chorionic cells - whilst the cell-body is much larger than the cells of Langhans' layer, the nucleus is smaller.

Another fact of some importance is seen in the absence, in the groups, of syncytial buds. They correspond, in other words, to endothelial cells which have undergone marked proliferation, the newly formed cells enlarging in a decidua-like manner. In other regions there is present a decidual enlargement of the endothelial elements without a co-existing proliferation.

DECIDUAL CHANGES in the PERITONEAL ENDOTHELIUM.

In two of my pregnant tubes I have detected a marked enlargement of the cells of the peritoneal covering. The detection of the change in this site is important in view of the fact that there is a vagueness in the literature regarding the possibility of its occurrence. I refer to it more especially in this place to emphasise a fact of considerable importance in connection with this research, namely the close resemblance existing between the endothelial and the connective tissue cells in their mode of reaction to the presence of the/

the foetal elements.

I have already elsewhere described a decidua-like enlargement of the peritoneal endothelium as found in one of my specimens (3 months pregnancy). In this case the peritoneal covering had disappeared in most places; where present it was found to exhibit the change. Since recording this specimen I have had the opportunity of studying another, in which the change is much more evident. The age of this specimen was impossible to determine because of the fact that the foetal remains were broken up by haemorrhage. The appearances present suggest that it must have corresponded to a very early pregnancy, in all probability situated in an accessory ostium in the upper aspect of the tube. The remains of such a structure are distinctly discernable incorporated with the tubal wall and are found to encircle the foetal remains. The probability of the pregnancy being of this nature is corroborated by the existence of a distinct accessory ostium in the opposite tube, which was removed at the same time. I mention these facts as they suggest a likely explanation of the peritoneal changes present. Situated as it was on the outer aspect of the tubal wall in a sac, the walls of which have broken down, there/

there had been an early oozing of blood into the peritoneal cavity, in all probability carrying with it the chemical substance secreted by the cells of the foetus. The blood escape must have been gradual and the peritoneal aspect was probably thus brought for some time under the continual influence of the chorionic cells, with the production of the changes to be recorded. Under ordinary circumstances there is usually in the pregnant tube a more or less complete detachment of the peritoneal endothelial covering due to the softening process. This is, in my experience, almost invariably the case after the pregnancy has advanced beyond a few weeks.

Round a large part of the circumference of the specimen under discussion the peritoneal endothelium is well-retained. On figure 107 the complete tube in transverse section is shown. In the mass of blood clot on the upper aspect the foetal remains are present. The dark line indicates the sites in which the endothelium of the peritoneal surface was present. The cells are everywhere enlarged, sometimes to a marked degree and here again the increase in size has involved the cell-body to a greater degree than the nucleus, the characteristic change/

change in the ordinary decidual cell of the pregnant uterus. The cell substance is distinctly granular as in the typical decidual cell. As in their swelling the cells have been closely packed together they have assumed a cubical or a columnar shape, and the surface of the tube thus appears as if covered by a continuous epithelium. (figures 105-6) In many places the change is associated with a rugosity of the tubal surface. This is due partly to the existence of distinct villous protuberances, & partly to the fact that the swollen endothelial cells have dipped down into the superficial part of the tubal wall. The papillary projections sometimes attain a considerable size and may here and there be seen cut across transversely and appear to be lying free.

That these appearances are not due merely to a warping of the surface by the increase in the endothelial area in consequence of the swelling of the individual cells is proved by the existence of distinct evidence of a cellular proliferation. In many places the cells are seen to be several layers deep (figure 105). The changes present, then, are to be attributed to two distinct factors, an increase in the size and an active proliferation of the cells. The cellular enlargement would seem without doubt to correspond to the decidual increase in size of the uterine/

uterine stroma cells during pregnancy.

A study of the changes, which the endothelial and the connective tissue cells of the tubal wall exhibit in response to the influence of the engrafted ovum, has demonstrated that in respect of the two important cellular alterations induced the two classes of cells coincide. In each type of cell there may occur a vacuolation of the cell substance due to an active fluid imbibition or there may be a great increase in size similar to what occurs in the pregnant uterus. I have suggested on a previous page that it is probable that these two changes, so different in their results, may in their origin correspond to the same common factor. In the one case the fluid imbibed has accumulated in the cell unchanged, in the other it may contain more albuminous matter which is precipitated or is built up into the cell body. Be this as it may, I maintain that the complete similarity of the results in each case dependent on the foetal influence is strong evidence in support of the conception that the two classes of cell are structurally alike. This idea is, as I have shown, confirmed by the finding that the connective tissue elements may take part in the formation of a new endothelium.

DECIDUAL/

DECIDUAL CHANGES in UTERINE WALL in
CASE of PLACENTAL RETENTION.

In the one specimen in which I have been able to study the changes induced in the uterine wall by the influence of placental fragments which have been retained, I have found the presence of a well-marked decidual reaction. This is evident in a portion of the mucosa, adjacent to the villi. Most of the structure has disappeared in the specimen, and the villi came close up to the muscular wall. In no place was there an actual invasion of the muscle.

There is a well-marked enlargement of many of the inter-muscular connective tissue cells.

The cell-body, here again, is involved in the increase more than the nucleus. In some instances the altered cells are found in clumps, in other places they lie imbedded singly in the muscular bundles. (figures 170-2). The cells are indistinguishable in size and structure from the ordinary decidual cell.

In this specimen, as in the pregnant tube, the appearances favour the conception that the process which has determined the dropsical accumulation in the connective tissue cells is to be identified with/

with that which, in other cases, causes a decidual increase. Here again in the same small area of the muscular tissue, cells exhibiting the former change are found close to cells exhibiting the latter. In many places, also the muscle fibres are seen to be separated by clear spaces, which, with a low-power lens look like decidual cells, but which, under higher magnification are seen to be unoccupied by a definite cellular material. In many of these spaces nuclei are lying and the appearances seem to be due to inter-muscular connective tissue cells which have been the seat of a fluid distension. (Figure 170).

In many regions of the muscular wall there are large multi-nucleated cells, similar to those found in the decidua serotina. The fact that these are found scattered irregularly through the muscle, and often between the muscular bundles at a distance from the sites of the villous attachments lends favour to the conception that they are maternal in origin. Such would seem also to be the most recent interpretation of the similar multi-nucleated cell masses seen in the serotina in normal pregnancy. (Figure 173).

Another observation of considerable importance from the point of view of the decidual formation/

formation in this condition is seen in the fact that, whereas in the uterine wall even at a distance from the chorionic cells there may be a marked haemorrhagic escape from the vessels where these are unsupported by a definite decidual change in the surrounding tissue, in the proximity of the foetal cells this alteration in the neighbouring connective tissue elements seems to protect the vessels against the blood escape. (Figure 115).

DECIDUAL CHANGES in CHORION-EPITHELIO- MATOUS UTERUS

THE ENDOMETRIUM.

Where this is retained the stroma walls are in places enlarged in a decidual manner. The uterine mucosa was preserved in only two of my specimens and in them only in fragments.

THE MUSCULAR WALL.

Throughout the muscular coat the connective tissue cells exhibit this change to a well-marked degree. The cells are in most cases easily distinguished from the foetal cells with which they may be intermingled, by the larger size of the cell-body/

cell-body and the smaller size of the nucleus. In some places it is more difficult to determine with accuracy the origin of the cellular elements; this is especially true in the maternal tissue immediately adjacent to a clump of the foetal cells. As I have already mentioned in all cases where there was the least difficulty in recognition I have, for the purpose of meeting critical objections, in describing the manner in which the blood escapes from the vessels, assumed that the doubtful cells were foetal in origin.

The decidual cells are in some places closely set together to form masses of considerable size (Figure 176), in other cases they are found singly in the muscle bundles (Figure 177). In most places the nuclei are small and the cell body takes on a faint stain. In some instances, however, the nuclei may be large, even bigger than those of the Langhans' cells. That these correspond to maternal cells is indicated by their site: they are scattered about irregularly in the muscular tissue and often at a considerable distance from the regions of the tumour masses. Two observations which prove their identity without doubt are the fact that the cell body is much larger than that of even the largest foetal/

foetal cells, and the fact that in their proximity the muscular tissue is not disintegrated to the extent invariably present in the neighbourhood of the chorionic cells. Here again it is interesting to note that where the change has occurred the oedematous ploughing up of the tissues, which is present in other regions, is absent. Even in the neighbourhood of the foetal cells, also, the decidual enlargement of the connective tissue cells has prevented the teasing asunder of, and the haemorrhagic escape from, the maternal vessels. (Figure 176). In the uterine wall there is the same dropsical distension of the cells, which we have noted in the other regions of chorionic activity. The fact that the two changes exhibited by the connective tissue elements, namely a decidual enlargement and a fluid imbibition, are somewhat similar in their nature, though differing in their results, is suggested by finding the two cellular alterations side by side in the same small area of the uterine wall. In each case the change is associated with a swelling of the cell body, and in each case it is obvious that the condition is due to the same influence, namely a protoplasmic change induced by the chorionic activity. In one point there is a difference between the two kinds of structural change produced in the cells by the process causing/

causing an increase in the size. Whereas in the decidual cell the nucleus is more or less centrally placed, in the cell the seat of a fluid imbibition the nucleus is usually pushed to the periphery of the cell-body, where it may be markedly flattened.

In the chorion-epitheliomatous uterus, as in the case of the placental remnants, there is found an abundance of very large cells with a large nucleus. Both cell substance and nuclear substance usually stain faintly. Here again I believe that these cells are maternal in origin; they differ in structure from the chorionic elements (Langhans' cells and Syncytium) and they are often situated between the muscular fibres at a long distance from the site of the foetal invasion. The muscle in their immediate proximity is, as before, often well-preserved.

I am convinced that they correspond to altered connective tissue cells.

In the uterine wall, also, there are detected large multinucleated cells, similar to those present in the decidua serotina in normal pregnancy, and identical to those scattered irregularly about the uterine muscle in the specimen exhibiting the effects of placental remains. Here again I believe their origin from maternal connective tissue cells is likely.

THE DECIDUAL MEMBRANE OF NORMAL PREGNANCY.

This structure, as is well-known, is composed of the mucous membrane, which, during pregnancy, becomes greatly thickened throughout the entire extent of the uterine body. The change, except in very rare instances, ceases at the level of the internal os. The increase is due almost entirely to the changes in the stroma elements. These become markedly enlarged to form the decidual cells. This change is most marked in the outermost region of the mucosa, which becomes the compacta. Here the main substance consists of the altered cells and the blood-vessels. There are few or no gland remains. In the deeper part of the mucosa there is a marked glandular hyperplasia and dilatation, transforming this region into the decidua spongiosa. In the tissue bridges between the expanded glands the alteration in the stroma cells is usually less marked than in the compact layer.

The decidua reflexa is the part of the uterine mucosa which intervenes between the implantation cavity and the uterine lumen. The decidua serotina separates the foetus from the muscular wall of the uterus, and from it the maternal part of the placenta/

placenta is formed. The decidua vera corresponds to the part of the altered mucosa not in direct relation with the foetal structures. It forms, in the early months, the main part of the decidual membrane, and consists of that portion of the thickened mucous membrane not comprised within the former two. Without touching on many of the aspects of the decidual membrane, which are described in the text-books on obstetrics, I shall pass on to consider it from the points of view which more particularly concern this investigation. I wish to approach the discussion of the subject under three headings:

- (1) The Factors responsible for the decidual change
- (2) The Structure of the decidual membrane.
- (3) The Function of the decidual membrane.

FACTORS RESPONSIBLE FOR DECIDUAL FORMATION.

The exact stages in the process of the decidual alteration of the uterine mucosa are still incompletely filled in. Of some points, however, we may be certain. In Peters' early ovum the decidual change is located entirely to the environment of the embryo. Even here the change must be considered to be in its earliest stage. In later embryos (Leopold, Merttens, etc., ⁽³⁾ ⁽¹⁴⁾) the decidual increase/

increase in the cells is still imperfectly developed, and even at the sixth week it is found well-marked only in the compact layer of the decidua vera

(Webster.⁽⁷⁾) The maximum development in the vera is attained at the end of the second month (Klein,⁽¹⁵⁾) between the second and third months (Webster,) or between the third and fourth months (Whitridge Williams.⁽¹⁶⁾) These observations prove beyond doubt that the change progresses up to a certain point with the duration of pregnancy. The conditions present in Peters' specimen justify the conclusion that the decidual increase is dependent on a stimulation of the stroma cells by some influence emanating from the foetal cells. This stimulus, at first located to the region of the engrafted ovum, soon extends the sphere of its influence. The more distant regions of the uterine mucosa come gradually under its sway, until, at the stage which corresponds to the completion of the decidual change, the foetal influence has reached the maximum of its power.

What are the nature and the source of this foetal influence and how is it disseminated? The exact nature of this influence is still a matter of conjecture, though there would seem to be little doubt that it consists of some substance of a chemical nature, probably a ferment or ferments, the results/

results of which are the complex of maternal tissue changes which characterise pregnancy. The origin of the influence which determines the decidual change we know with certainty. The fact that it is well-marked in the maternal tissues where only the chorionic cellular layers are present e.g. chorion epithelioma, proves beyond doubt that it originates in the ectodermic cells, and not in the foetus or the mesoblast of the chorion. As regards the mode of its dissemination to regions distant from the actual site of the ovum it is clear that this may be accomplished in one or other of both of two ways. It may be due to a passage by direct extension through the tissues, by a process of diffusion, or it may be carried by the blood stream. In support of the first mode of transmission is the fact that in Peters' early ovum the change which is present in the mucosa only in the proximity of the chorion, has, however, involved the tissues at some little distance from the embryo. It may, however, be urged that here the transference was by the blood stream and that, in this early stage, the influence becomes quickly diluted as it leaves the chorion. The fact, however, that in tubal pregnancy the wall of the tube is invariably the seat of the degenerative and decidual changes at a considerable distance/

distance from the ovum bed, and that, in the process, both the arteries and veins are affected, would prove beyond doubt that there must be a certain amount of direct diffusion through the tissues. The same is seen in chorion-epithelioma. On the other hand, the extensive involvement of the uterine mucosa in the decidual change would suggest that there must be a certain degree of blood dissemination. This fact is also suggested by the occurrence of a decidual transformation of the mucosa of the uterus or of the opposite tube in tubal pregnancy and of the occasional development of a decidual change in the tube in uterine pregnancy. It would seem that to satisfactorily account for these phenomena we must admit the occurrence of a spread of the chorionic influence by the blood stream; this conception is, moreover, consonant with the fact that during pregnancy there take place many and marked tissue changes in distant parts of the body e.g., mammary signs, thyroid enlargement, etc.,

The occurrence of a decidual change in pregnancy in the mucosa of the uterine body and except in rare instances, its absence in the cervix, and distant regions, and its occurrence in a marked degree only in the uterine mucosa and the tubal mucosa in many cases of tubal pregnancy, demonstrate beyond doubt/

doubt that for its development there must be a susceptibility on the part of the tissues. The structural necessity for the presence of a well-marked decidual reaction is that the tissue must approximate in character to that of the uterine mucosa. This essential is presented only by the mucosa of the tube. In each case the stroma is of a peculiar, undifferentiated embryonic type. We have seen that it is the soft displacable nature of this tissue which permits, in the uterus, of the ready opening up of the vessels and an oedematous and haemorrhagic escape into the stroma during menstruation, and, in all probability, during pregnancy. Does it not seem strange, to say the least of it, that the only region where, in normal pregnancy, the blood and dropsical escape has occurred to any extent is the vicinity of the embryonic structures, whereas, as is seen in menstruation, the uterine mucosa is obviously constructed to allow of a ready blood escape at any part of its surface? Does not the coincidence, namely the existence of a blood escape which is definitely localised in one place, the other regions of the stroma remaining blood-free, assume proportions which are remarkable when we note that the extraordinary increase in the stroma cells, which occurs during the decidual change, would seem to/

to be able to effectually prevent such a blood escape except in the region of the implantation cavity, if there were any tendency to its occurrence? This question I shall again raise in the next section of this investigation.

S U M M A R Y .

The decidual increase in the stroma cells of the uterine mucosa during pregnancy is traceable to some influence, probably bio-chemical in nature (enzyme) emanating from the chorionic cells. This stimulus reaches the cells of the stroma either by a direct spread through the tissues from the region of the foetal cells, or by transmission along the blood stream.

STRUCTURE of the UTERINE DECIDUA.

My specimens have afforded me the opportunity of observing some points of especial interest and importance in connection with the investigations previously recorded on the structure of the vessels of the endometrium, and on the changes which are associated with a decidual formation in abnormal locations, especially the pregnant tube.

In an enlargement of the stroma cells in the decidua vera many differences in the resulting changes are found. In some cases the cells are round, oval, or polygonal in shape, in other instances they are spindle-shaped, often being drawn out to a remarkable/

remarkable degree. In some cases they are separated from one another by distinct spaces and they are then often seen to be united by protoplasmic outrunners of the cell bodies. The intervening spaces may be clear or they may occupied by a granular or fibrillar material which stains with eosin. It is probably coagulated serum. In many places leucocytes and cells, which look like unaltered stroma elements, are seen lying between the decidual cells. Between these smaller cells and the largest decidual elements, it is easy to detect all gradations in size. By some observers (Marchand (17) Rossi-Doria (13)), these appearances indicate active transformation of the one size of cell into the other. They have described mitotic figures which would indicate that there is associated with the change an active proliferation. Whilst my specimens confirm their interpretation of the role of the smaller cells, I have been unable to detect the presence of the mitosis. On the other hand, in many places cells with double nuclei are visible, which, in several instances, would seem to have been formed by a process of direct nuclear division (Figures 132-3). On the question of the possible occurrence of a mitotic division in the decidua my specimens comprising as they do only three complete decidual membranes, the youngest of which corresponds to a pregnancy/

pregnancy of $2\frac{1}{2}$ months, do not permit of a definite pronouncement. The fact, however, that there is evidence of a proliferative change associated with the decidual increase in size of the cells would tend to bring these observations in line with those recorded in connection with the pregnant tube. We there saw, in some locations, a distinct hyperplastic change conjoined with the decidual enlargement of the cells. In the respect just mentioned my specimens accord with the changes described by many other observers.

In many regions of the decidual membrane the cells are packed close together and the shapes they assume are obviously due to mechanical pressure against one another. The degree of expansion of the cells, which varies within wide limits, would seem likewise to be determined in some places by factors purely mechanical in nature. For example it is often possible to detect a smaller cell wedged tightly between surrounding larger cells, whose size would seem to have prevented its further expansion

In many places the cells have attained an enormous size and then they are usually seen to be packed tightly together. (Figure 182) Between the distended glands in the spongiosa, on the other hand, the/

the same dense packing together is often seen where the cells are comparatively small.

Here again mechanical influences have been at work, the small tissue bridge precluding an opening out which is essential to the cellular expansion if it is to occur to any marked extent. As a general rule in my specimens the cells in the spongy part of the decidua are smaller than they are in the compacta. Another factor, also mechanical in nature may explain this. As has been shown by several observers the decidual change in a given area of the mucosa progresses from the surface inwards. The increase in size of the outermost cells is allowed to occur at an advantage, because of the ease with which the surface of the mucosa can become displaced towards the uterine cavity & the area of the corresponding part of the mucosa is allowed to increase. These changes are seen in the marked projections and undulations on the surface of the decidua. In view of these facts it is obvious that the deepest parts of the mucosa, under ordinary circumstances the best supported because of their situation, are still further prohibited from an increase in size by the decidual increase in the superjacent stroma. I believe that this amply explains the fact that the spongiosa/

spongiosa cells are usually smaller than those of the compact layer. I mention these facts because of their bearing on the decidual changes which are seen in the vessel walls.

In the section devoted to an investigation of the structure of the endometrium I advanced the belief that the entire extent of the stroma, including the intimal and outer cells of the vascular walls, is composed of an undifferentiated embryonic material, connective tissue in nature. In support of that view I was able to demonstrate, I believe without doubt, the structural similarity between the endothelium and the stroma. It was shown, also, that during menstruation the intimal cells are easily separated from one another and, with the surrounding stroma, are often displaced to form the walls of a newly-formed blood space. This process is often associated with a suffusion of the surrounding tissues with fluid and red cells. The same observations were shown to apply to the outer supporting cells of the vessel wall. In the mucosa, except at the part immediately abutting on the muscle, there is an absence of elastic or muscular tissue in the vessel walls.

The study of the pregnant tube and of the chorion-epitheliomatous uterus was found to give additional/

additional support to the conception that the endothelium and stroma cells of the mucosa are structurally identical. In these regions we found this similarity again appearing in the perfect resemblance between the two elements in their response to the chorionic influence. In each there was apt to be a fluid imbibition or a decidual enlargement, and in some cases the connective tissue cells were seen to function as endothelium.

Do those observations coincide with the appearances revealed in the decidual membrane? It is clear that, in the marked deviation of the mucosa from the ordinary condition which characterises the pregnant state, we should have an opportunity of putting the above interpretation to the test.

In many places the blood-vessels are lined with cells which correspond in every respect to those in the surrounding decidual tissue. This is chiefly the case in the distended vessels. In these the decidua may come right up to the blood. In other vessels, and this is the usual condition, the lining layer is formed by flattened and elongated cells, similar to the endothelium in the resting state. It is obvious that the former appearance is due either to the fact that the endothelial cells
of/

of the blood space have been detached and have disappeared or to the fact that they have become enlarged in a decidua like manner. If the latter interpretation be true the existence of an unaltered endothelium in the case of other vessels must, in all probability, be due to some difference in circumstance which has determined the retention by the cells of their wonted size and shape.

If the endothelial cells in the uterine mucosa are immune to the decidual changes they must differ in their structure and their mode of response to the chorionic influence from the endothelial cells in the tube. Here we saw in many places a definite enlargement of the cellular elements in a decidual manner and this both in the vascular endothelium and that in relation to the peritoneal surface. That there does exist such a structural difference between the endothelium in the two sites is, on the face of it, unlikely. The exact similarity between the two structures in their reaction to the foetal influence is, moreover, not difficult to demonstrate. In proof of this I submit the following observations:-

- (1) In many places, as I have said, the vessel lumina are found to be lined by a layer of cells similar in every respect to the surrounding decidual elements. (Figures 106-7) It is/

is unlikely that this appearance is due to a detachment and disappearance of the unaltered endothelium because, whereas in the same sections many of the vessels are lined by cells apparently unchanged, there is no trace of the process in action. Under these circumstances one would expect to find in some locations a cellular separation occurring if by this means we are to explain the appearances.

- (2) In many places one can actually see the decidual enlargement of the cells in the process of occurrence. On Figure 188 is seen a vessel from the decidua vera on the side of the uterus opposite to that occupied by the placenta. Here we see a marked proliferation of the endothelial lining, which has resulted in the projection into the vessel lumen of masses of the cells. Their appearance negatives the possibility, which otherwise might have been entertained, that they are chorionic cells. The nuclei are smaller, and in staining reactions they correspond to the surrounding decidual cells. Their site, also, throws this interpretation completely/

completely out of court. The cellular mass can be traced through a number of sections, and the change can be detected throughout a long extent of this vessel. It can also be seen in several other of the vessels. So far as I know it has not previously been described in the decidua vera.

The appearance obviously indicates the presence of an active endothelial proliferation. The point to which, however, I wish to direct special attention is the large size attained by the cells, many of which are as large as some of the increased cells in the adjacent decidua. The change is, without doubt, of the same nature as that exhibited by the elements of the stroma. The explanation of the fact that in this region they have not enlarged to the enormous degree exhibited by some of the surrounding decidual cells is probably to be found in the mechanical packing together which has occurred. This I shall refer to again. The division of the cells is, in all likelihood, by an amitotic nuclear fission. In no place could I detect mitotic figures. In many of the cells the nuclear division can be seen in the process. In this respect, again, they thus coincide with the surrounding/

surrounding stroma elements, where the same nuclear changes are present.

In some sections, also, I have been able to detect similar changes in the vessels in the muscular coat. In figure 190 is represented such a vessel. This was present in a different specimen. Here there is seen on either side a cellular mass projecting into the vessel lumen. The masses are attached to the vessel wall and are obviously endothelial in origin. In appearance and staining they differ widely from the foetal cells. In this specimen they have undergone a greater degree of enlargement than in the last specimen. They are undoubtedly to be looked upon as decidual cells. In another part of the same vessel the endothelial vacuolation, to which I have repeatedly referred, is to be seen. The wall of the vessel and the surrounding tissues in this case are involved in an oedematous escape. The same changes are seen in figure 167.

The observations seem to me to demonstrate beyond doubt that the uterine endothelium has the faculty of exhibiting a decidual change in a manner as perfect as that of the stroma cells. As in the stroma it is clear that here, also, the decidual alteration is intimately bound up with a definite proliferative/

the stroma. (Figures 188&191) The cells are often elongated and spindle-shaped and arranged round the vessel in concentric circles; the individual cells often become wider and wider as the vessel is left. Of course in these cases the enlargement may have occurred in the other cell diameters and the appearances we see may correspond to sections across enlarged cell discs. Be this as it may, the resulting appearances would seem to prove beyond doubt the great importance of purely mechanical influences. Another point of the very greatest importance in this connection is to be found in the fact, which is easily understood, that in the expansion which accompanies the decidual increase the looser tissues of the stroma are involved before the more condensed structures in the vessel proximity. In this region, we shall recollect, the condensation increases towards the vessel lumen. This fact would seem amply to account for the conditions present - the stiffening of the perivascular tissues which must occur during the decidual change will tend to block the way for the process in the tissues immediately adjoining the vessel wall and in the vessel wall itself. This result forms the counterpart of what we have seen to occur during a teasing asunder of the vessel/

vessel walls and stroma during menstruation, where in the case of a well-supported vessel the detachment occurs in concentric layers, the process gradually advancing inwards to the endothelial lining.

These considerations must explain to some extent, also, why in many cases the stroma cells forming the vessel wall, especially in a well-supported vessel, often do not exhibit a decidual enlargement at all.

The effects of mechanical factors is well seen by a study of figure 19 where we see a gradual diminution in the obvious decidual increase in the cells as the endothelial layer is approached.

It seems to me that we must look to the above-noted facts for an explanation of the absence of the decidual increase in the endothelium in many cases. The better supported the surrounding stroma and vessel wall the less the chance of a decidual enlargement occurring. It would be just as irrational, in view of what we have previously learnt, to say that, because the endothelium does not exhibit the change in some instances, it therefore differs structurally from the other endothelium and the stroma where the change is present, as it would be to declare that the stroma elements which fail to exhibit the increase diverge structurally and functionally/

functionally from their neighbours, which exhibit the process. In conclusion I would submit as strong confirmatory evidence of my contention the fact that, for the most part, the decidual increase in the endothelial cells is most evident in the expanded vessels and the vessels in which the decidual enlargement of the stroma has involved the entire thickness of the vessel wall. These are obviously vessels in which the opening out of the stroma has occurred to the greatest advantage.

S U M M A R Y.

- (1) The investigations support the observations of previous workers that, in conjunction with the decidual enlargement of the stroma cells, there is present an active proliferative change. The cell division is by amitosis.
- (2) Mechanical influences explain many of the variations in size and shape of the cells.
- (3) There may occur a true decidual change in the endothelium of the mucosa vessels and also those of the muscular coat. Here we have evidence both of enlargement and proliferation by direct cellular division. These observations complete the evidence in favour of the structural identity of the endothelium and the stroma cells of the uterine mucosa.
- (4) Where an obvious decidual change in the endothelium is absent this is due to mechanical influences.

THE/

THE FUNCTIONS OF THE DECIDUAL MEMBRANE.

The theories advanced in the literature to explain the functions of the uterine decidua may be grouped under one or other of two headings: (1) it is laid down as a barrier against excessive foetal invasion of the maternal tissues, (2) it serves as a storehouse for nutriment, which is absorbed by the growing foetal cells. The orthodox conception of the probable functions of the decidua is thus expressed by Whitridge Williams in his text-book of Obstetrics (1908): "the function of the decidua may not merely be to afford a suitable structure for the implantation and nutrition of the ovum, but also to protect the maternal organism against invasion by foetal tissues". The idea that the decidual cells have a nutritional function to perform is to some extent supported by the results of histological and experimental researches in the lower animals. It would seem not unlikely that the decidua has in some animals (rabbit) a definite function to perform in connection with the glycogenic metabolism (Bernard, (19) (20) (21) (22) (23) Godet, Maximow, Chipman, Lochead etc.) The cells in the maternal part of the placenta are seen to act as/

as a secretory mechanism and a storehouse for glycogen which is apparently directly taken up by the advancing foetal elements. The same may be true for (24) fat (Eden, Chipman etc.,) and other food substances.

The other explanation of the decidual function, namely that it prevents an excessive foetal invasion, is in a sense directly antithetic to that just mentioned. In the one case the cells act as a deterrent to the chorionic growth, in the other case, by providing nutrition, they would actually foster this growth. Neither of these explanations accounts for the presence of the decidua vera. The decidua serotina, I believe, contributes largely to the limitation of the growth of the foetal ectoderm into the maternal tissues, but in a different manner than is usually believed. The decidua reflexa clearly serves the function of shutting in the embryonic cavity and the intervillous blood space. In view of the early atrophy of the foetal villi in relation to this part of the decidua it is impossible to conceive that the complete transformation of the uterine mucosa to form the vera is for the purpose of preventing a wholesale invasion of the uterine wall. The fact that so far this part of the altered mucosa has not been associated with a definite function is candidly/

candidly admitted in the following words: "We are unacquainted with the functions of the decidua vera" (Eden - Manual of midwifery, 1908.)

It seems to me that the probable nature of these functions is to be found in the investigations which I have recorded in connection with the mode of the chorionic action on the maternal tissues. The precise nature of this activity we have seen in the abnormal regions studied, and the conception that in the uterine mucosa the same processes are in operation has been reinforced by the study of the early decidua, especially in the cases of Peters and Bryce and Teacher, and the appearances detected in the decidual membrane of a later date.

I have shown that in the pregnant tube, and in the uterine wall, the seat either of a simple or a malignant chorionic involvement, definite tissue and vascular changes were present. These consisted in a wide spread oedematous and blood escape from the vessels, associated in many cases with a wholesale teasing asunder of the vessel walls, and a gradually increasing expansion of their cavity. These conditions, whilst most marked in the immediate vicinity of the foetal ectoderm, were present even at a considerable distance from this. The chorionic influence, /

influence, in all probability to be identified with an enzyme or enzymes, has led to a softening and solution of the muscle, and, what is more important in so far as the analogy with the uterus is concerned, to an active imbibition of fluid by the connective tissue elements. In all these locations I have pointed out that a decidual change in the surrounding connective tissue elements tends to prevent these irregular and uncontrolled vessel and tissue changes. The influence of this decidual change was demonstrated in a manner which leaves little room for doubt in the pregnant tube. Here it was found that the only regions of the tubal wall which had resisted the changes were those with a decidual enlargement of the connective tissue cells. This in some cases was present in the vessel wall. (Figures 99-101) In other cases it was present in the tubal folds. On plate & figures 95-96 are shewn a representation of the conditions present. Whilst the muscular coats, and the thick walls of a large vein are opened out by oedema and blood dragged out as the result of the tissue changes and this even at a considerable distance from the embryo, the stiffening of the connective tissue of the mucosa by the marked decidual enlargement of the cells has completely prevented /

prevented the process. It seems clear that this is due to the mechanical support given to the vessel walls and the surrounding tissue by the dense packing of the altered cells.

Is there any evidence that such a function is subserved by the uterine decidua? Here we have seen there are changes which indicate the existence of protoplasmic changes of the same nature as those which have, in the other sites, led to an uncontrollable blood escape and an irregular and increasing vascular expansion. That here also the decidual packing of the cells is intended for a limitation of these changes is convincingly demonstrated by a comparison of the maternal tissues in the neighbourhood of the ovum in Peters' case with those in an embryo with a more marked maternal reaction e.g., Bryce - Teacher. Whilst in the former, where the decidual process is in its initial stage, there is a wholesale & irregular ploughing up of the immediate tissues by fluid and blood, and an enormous vascular distension, in the latter the changes, though present to some extent, are much more limited. In a still later stage they become completely lost. Figure 155, taken from one of Bryce and Teacher's plates, indicates clearly the influence of the decidual change when it is/

is contrasted with one of Peter's plates representing the same relative position. (Figure 153.)

The ultimate cellular changes associated with the decidual condition are still beyond our grasp; any explanation must be in the main conjectural. It would seem, however, clear that the increase in the cell contents associated with the change must be derived from the blood. In fact we are inevitably forced to the conclusion that in the change we have a positive indication of a tissue alteration which has resulted in an active and an extensive imbibition of fluid from the blood stream. This may be directly furnished by the blood-vessels or it may partly be lymphatic in origin. In this consideration it seems to me that so far we have a strong analogy with the process which I have advanced to explain the manner in which the maternal vessels are opened up during pregnancy. This I have indicated is probably dependent on protoplasmic tissue changes which determine an active imbibition of the blood (fluid and corpuscles) by the uterine stroma. The analogy between the two processes ceases at the immediately succeeding stage, for whereas in the one case the fluid absorbed remains unaltered in consistence and as such can pass freely through the tissues, in the other it is built up by the cell into its substance./

substance. The necessity of this is obvious - it prevents the oedematous teasing out of the vessel wall and the occurrence of an irregular blood infiltration at regions where its presence would be not only unnecessary but injurious.

The exact manner in which the change advances in the decidua vera is still imperfectly worked out. Different observations in early cases would tend to indicate that it commences in the surface part of the mucosa and advances in an outward direction towards the spongiosa. This would seem to be due to the fact that in the superficial parts a spreading out of the stroma is more easily accomplished (cf. menstruation and many pathological conditions.) Here also the vessel walls are thinner and correspondingly easier of separation with a permission of the fluid escape.

In some of the lower animals, e.g., rabbit, the decidual transformation of the cells begins in the immediate vicinity of the vessels and advances steadily in an outward direction till the complete decidual surface is formed. This appearance is easily understood in view of the fact that the necessary fluid is derived from the blood stream. The cells in all probability immediately assume the decidual/

decidual state as they receive the means of doing so. The condition present in these cases strongly suggests the existence of a measure intended for the support of the vessel wall. Does the change in the human stroma also begin in the vascular regions? If my views be correct it seems not unlikely that such is the case. In this connection I shall await the results of future investigations with interest.

What is the significance of the proliferative change present? As has been suggested by other observers it may indicate the means by which the stroma is recuperated for the death of the decidual elements, many of which, especially after the first few months, are seen to be degenerating. Or it may be (and both purposes are probably thereby served) an accessory means by which the decidua undergoes the increase in length necessary to keep apace with the increase in the uterine cavity.

DECIDUA SEROTINA.

If the conclusions just formulated be justified we are enabled to appreciate the manner in which the foetal elements are prevented from irregularly infiltrating the maternal tissues. We shall, perhaps, /

perhaps, better understand this by recalling the analogies presented by the pregnant tube and the foetal invasion of the maternal structures seen in chorion-epithelioma. When a mass of the foetal elements in either of these regions comes into contact with the mother's tissue there occurs a softening and in many cases, especially where muscle is included, an actual solution. The important result of this action from our point of view is that there is an active imbibition of fluid by the affected part. This may be derived either from the space in which the chorionic cells lie (e.g. a vessel) or it may be passed across the tissue intervening between these and a neighbouring vessel. In either case the essential element for the nourishment and growth of the foetal cells (i.e. the blood fluid) is obtained. It is therefore the presence of maternal fluid or blood at a given point which determines the chorionic increase.

In the decidua the change in the cells has prevented this softening and fluid infiltration of the tissues. For this reason the food necessary for the growth of the foetal elements into their midst is wanting. When they come into contact with the resistant tissues their development is arrested.

We/

We thus see that the decidual change, which is provoked by the foetal influence, has in this region functioned in exactly the same manner as in the other decidual regions i.e., it has prevented the tendency to an active transference of fluid into and through the tissues. We thus see that the function of the serotina is to act as a barrier to the foetal invasion but only in so far as we have indicated.

The rationale of this action is clearly indicated by comparing the effects of the chorionic activity in the pregnant tube and in chorion-epithelioma with those present in the decidual membrane. I have referred to the softening and fluid separation of the tissues which occurs in advance of the chorionic cells in the former cases. In the vessels this fluid imbibition is often associated with an aneurismal expansion of their lumen - the walls in the process receding from the foetal cells where these are in the cavity. Teacher, who, I believe, first described this condition, rightly saw in it an analogy to what occurs in the production of the normal implantation cavity of the ovum. His interpretation of the details of this analogy I have advanced reasons to show was imperfect. I have pointed out that the change is by no means confined to/

to vessels containing the foetal elements. It is widespread and it is often seen to result in a wholesale advancing of the vessel spaces toward the chorionic cells. (cf. Peters' ovum.) It seems to me that this latter process more accurately accords with the manner of production of the implantation cavity, that it is an opening out of the tissues in advance of, rather than a destruction by, the embryonic cells. This idea I have shown conforms with Peters' specimen.

If such be the case we have a further explanation of the decidual function. As shown by the Bryce-Teacher specimen it early reaches a degree in the vicinity of the ovum well-nigh perfect. It must then prevent a further increase in the implantation chamber in the way we have mentioned, and which is associated with a displacement and thinning of the underlying stroma. The enlargement of the cavity then must be due, not to a destruction, but to a hypertrophy, of the walls, (decidua and muscle.) This it seems to me is absolutely certain. If it were otherwise the uterine wall would soon be thinned out and destroyed. We can now appreciate the importance of the proliferative change. By an increase in the decidual and the muscular elements there/

there occurs the gradual expansion of the uterine wall and the enclosed gestation cavity.

The effects of the decidual change in preventing the above-mentioned tissue softening and displacement is well shown by comparing figure 192, which shows a chorionic mass within and in contact with the walls of a decidual vessel, with the results seen in the case of a similar mass in a similar situation in the pregnant tube or in chorion epithelioma. If I am justified in the employment of the analogy, and I am, in this respect, following in the footsteps of most previous observers, it seems to me the demonstration is conclusive.

Whilst limiting the extent of the above-mentioned tissue changes, whilst preventing an excessive displacement and thinning out of the mucosa underlying the ovum, and, at the same time, an irregular fluid and blood infiltration of the stroma, the decidual change in no way interferes with the presence of the intervillous space, in which the foetal elements are richly supplied with the maternal blood, and in which they undergo the marked proliferative changes, which we associate with the human placenta. It is, at first sight, difficult to understand how it is that the enormous increase in the stroma in consequence of the decidual change, due to/

to the cellular enlargement and the cellular proliferation, does not encroach on and even obliterate the intervillous space. We have seen the change well-marked even in the very early stages of the imbedding process, when the implantation chamber scarcely measures 2 mm. in its longest diameter (Bryce-Teacher ovum.) The extraordinary increase in volume of the mucosa associated with the decidual alteration is emphasised when we remember that, not only does it increase pari passu with the increase in the length of the uterus, but it actually, in the early months, increases out of proportion to this. The difficulty, it seems to me, is the same as that associated with the fact, that, in spite of the increase in volume of the surrounding stroma, the vessel lumina are not encroached upon; at any rate, in the large majority of cases. What is the secret of this?

To account for these phenomena I would advance the following explanation. From what I have pointed out in a previous section of this investigation it seems likely that in a given area of the stroma the decidual increase in the cells only occurs to an extent strictly proportional to the degree in which there has occurred, or in which there tends to occur, /

occur, an opening out of the structures. This fact, I have shown, amply accounts for the absence of the change in the endothelium and the supporting cells of the more condensed vessel walls, and it accords with its occurrence in the vessels which seem to have opened out. If this be true then we can easily understand how it is that the integrity of the lumen is preserved. The same will apply to the intervillous space.

SUMMARY/

S U M M A R Y.

- (1) In the uterine mucous membrane and muscular coat during pregnancy there is evidence of a wide-spread tissue change tending to lead to an uncontrolled opening-up of the vessel walls with an irregular oedematous and haemorrhagic escape. It is present throughout the entire extent of the uterine wall, and it is due to the gradual extension of the chorionic influence from the embryonic site by a direct passage through the tissues or by a circulation along the blood stream.
- (2) Unlike what is found in the pregnant tube, in the uterine mucosa and muscular wall in the case of retained placental fragments and in chorion-epithelioma the haemorrhage and oedema in normal pregnancy are limited to the region of the embryo and to the immediate proximity of the vessels. The irregular and uncontrolled vascular expansion found in the abnormal regions of chorionic activity is limited in the case of the pregnant uterus.
- (3) In the abnormal regions the only sites where the limitation of these vascular and tissue changes has occurred are the places where there has/

has taken place a decidual enlargement of the connective tissue cells.

- (4) The uterine mucosa is especially constructed to permit of a ready occurrence of a blood escape at any part of its substance. This takes place periodically as a wide-spread cedema and haemorrhage during menstruation in response to some substance reaching it in the blood stream, which alters the protoplasm in such a way as to lead to an active imbibition of the blood fluid and corpuscles. We have seen that the same changes are apt to occur as the result of the chorionic influence and at a considerable distance from the foetal elements, where the amount of the liberated chorionic secretion must be much smaller than that spreading from the foetal structures during pregnancy, (placental fragments.) This special susceptibility of the uterine mucus membrane to these tissue changes must be controlled in some way during pregnancy. Otherwise there would inevitably be an cedematous and haemorrhagic escape throughout its entire extent.
- (5) As the result of these investigations, we are thus able to assert with the greatest possible certainty /

certainty that the function of the Decidual Membrane is to localise the vascular expansion and the fluid and blood escape to the region of the intervillous space. By so doing it limits the growth of the foetal structures entirely to the implantation cavity.

These facts explain why the entire mucous membrane exhibits the decidual change. The limitation of the vascular changes in the muscular wall is dependent on the well-marked muscular hypertrophy which occurs during pregnancy.

SECTION X.

PRELIMINARY ACCOUNT of VERY EARLY HUMAN OVUM.

SECOND EARLY OVUM. (lent by Dr. TEACHER).

A D D E N D U M.

Since writing the preceding pages I have had the opportunity of examining two specimens of early ova, and as they reveal evidence of the strongest confirmatory nature with regard to many of the conclusions formulated in the foregoing sections, I have thought it wise to include a short description of the more important appearances as an addendum to this thesis.

PRELIMINARY ACCOUNT OF A VERY EARLY HUMAN OVUM.

This specimen was discovered accidentally in a portion of decidua sent to the Royal College of Physicians Laboratory for examination on the 1st April, 1910. The early ovum was detected in one of the sections and, through the kindness of Dr. James Ritchie, it was handed over to me for further examination on the 9th April. A number of the sections containing the ovum were unfortunately lost but, as I shall subsequently point out, it would seem more than likely that in the part rescued we have the greater part of the ovum and that, therefore, we are in/

in a position to estimate its maximum diameters. As soon as the value of the specimen was recognised the portion of the paraffin block containing it was cut into an uninterrupted series of sections. By this means I have been able to obtain 42 sections containing the ovum. These were stained for the most part with haematoxylin and eosin. The preservation, considering the manner in which it was obtained, is fairly good.

HISTORY. The specimen was obtained from a patient aged 21. The last menstruation commenced on the 22nd February. The period due on the 21st March was missed. On the 31st March she complained of a slight bleeding discharge and on the morning of the 1st April passed the decidual fragments, in which the ovum was discovered. Previous menstruation somewhat irregular. No definite history as regards coitus obtainable.

GENERAL DESCRIPTION OF SPECIMEN. This consists of three pieces of thickened mucosa and some blood clot. Two of the fragments are extremely irregular in shape and in the course of the sections are seen to be somewhat broken up into different pieces. The portion of the mucous membrane containing the imbedded ovum, on the other hand, is more regular in shape. It is an elongated oval in contour, rounded off at one end/

end (Figure 193), whilst at the other it tapers off into a fine strand of the mucosa. As the sections are followed the oval becomes increasingly smaller until it ultimately disappears. After a few sections are passed, also, the tail-like process becomes lost. From this description it is, I think, clear that we are dealing with the elevated lobule of decidual tissue which corresponds to the similar structure present in all the other early ova (Teacher-Bryce, Peters, Leopold). In cutting the block the first sections correspond to the base of the lobule and have shaved the surrounding mucous surface (corresponding to the tail). The succeeding sections cut the lobule across at more and more superficial levels until it is ultimately lost altogether.

THE DECIDUA. In the outlying portions of mucosa there is an almost complete absence of a decidual change. In places, especially towards the more superficial parts, the stroma cells are enlarged. For the most part, however, they have retained their normal size. Throughout the entire extent of the mucosa there is a well-marked oedematous exudate, and in many places a haemorrhagic infiltration of the tissues. There is also an evident polymorphonuclear escape. The epithelium of the glands and surface has/

has in most places been shed.

In the decidual lobule in which the ovum is placed the same general features are present. Here there is a shedding of the superficial epithelium and of that lining many of the glands. The gland spaces are in places markedly expanded. In the lobule the implantation chamber containing the ovum is placed. It is shut in by a thin shell of the mucous membrane and is placed more toward the pole of the cut lobule which corresponds to the rounded free end at the base. The characters and size of the chamber and the ovum and some remarkable appearances which are divulged in the course of the serial sections will be discussed in the next paragraph.

The region of the decidua immediately bordering on the gestation cavity is undergoing a necrotic change - the cell outlines have disappeared, the nuclei are disintegrating and there is produced a more or less homogeneous structure deeply staining with eosin. In this, large numbers of well preserved red blood corpuscles are seen.

At no part of the lobule is there more than a poorly marked decidual change in the cells. In many/

many places, especially in the immediate proximity of the ovum cavity, the cells are enlarged, and in regions they may attain a size comparable to that associated with the typical decidual cell (Figure 194). The fact that the change is present to a very minor degree, and then only in the vicinity of the ovum, would seem to prove that we are dealing with a very early stage in the process.

As in the outlying portions of the mucous membrane there is here a marked cedematous and blood escape. In many places there is a distinct leucocytic infiltration of the tissues.

CHANGES IN THE VESSELS AND MODE OF THE BLOOD ESCAPE.

In view of the investigations recorded in the preceding part of this research the changes in the vessels and the manner in which the blood is escaping are of especial interest and importance.

In all parts there is a distension of many of the vessels. This is especially the case in the broad part of the decidual lobule which corresponds to the side of the implantation chamber (Figure 193). Here there is a number of expanded vessels, whose walls are very fine, being formed only by one or/

or two layers of cells. (Figures 195 & 196). This condition corresponds to the vascular change detected in all the youngest ova described. I have already referred to it in connection with the Peters, Teacher-Bryce, and Leopold ova. The fact that it is invariably present in the specimens no matter how obtained would indicate that it is to be considered as a normal change and is not due to the process of abortion, which, we shall recollect, was the manner in which my specimen was obtained.

As I have mentioned the walls of the distended vessels are thin and this is due to the fact that there has been a wholesale detachment and displacement of the surrounding stroma elements. These blood spaces thus correspond to the sinuses or distended capillaries which I have described in full in connection with the menstruating mucous membrane. In structure and in mode of formation they are identical, so far, at any rate, as the grosser changes are concerned. In other respects, also, the resemblance is emphasised. In the first place the opening-up of the stroma and vessel wall has, in many places, resulted in the creation of a complete gap between vessel lumen and surrounding tissue (Figure 196). The ease with which these changes occur in the uterine mucosa/

mucosa is, as I have recorded in a previous section, dependent on the peculiar structural conformation which it presents. In addition to these changes there is seen to be a wholesale exodus of the red cells through the wall into the surrounding tissue. The corpuscles are streaming out in every direction, both through the incompletely opened-up regions and at those places where there is a complete breach in continuity.

The blood leakage from the vessels is, as I have stated, found at a distance from the implantation chamber and where there are no foetal cells. In fact, as I shall describe on a succeeding page, at no point, except at the marginal necrotic area of the wall of the ovum cavity, was there any evidence of an incorporation of the foetal cells with the maternal tissue. Even here it is only rarely encountered. These facts thus force us to the conclusion that the opening up of the maternal vessels during pregnancy with the consequent haemorrhagic escape is due to some influence apart from a direct cellular invasion of the vessel wall with a mechanical escape of the contents. These appearances coincide with the process present in the abnormal regions of chorionic activity, which I have recorded on preceding pages, and in which the changes justified the conclusion/

conclusion that there were in existence active tissue changes determining an imbibition of the blood fluid and corpuscles, as opposed to a mechanical liberation of the vascular contents.

The resemblance between the conditions encountered in the pregnant tube etc., and those present here, is emphasised in a degree which is most convincing by the discovery that from the vessels opened up in the way I have just described the blood cells are actually seen to be streaming in quantity through the maternal tissue intervening between the vessel lumina and the implantation chamber. I maintain that these appearances prove beyond doubt what my researches on the pregnant tube, chorion-epithelioma etc., had previously led me to affirm, namely that the orthodox conception of the manner in which the growing embryo is furnished with the mother's blood must be completely modified. It is not due to a destruction of the vessel walls by the invading chorionic cells, neither is it due to a mechanical giving way of the vessel wall where this comes up against the advancing trophoblast (Peters). On the contrary the appearances just described prove that in the process there is in action some change in the vessel/

vessel wall or tissue leading to a wholesale leakage of the corpuscles, even through a wall which is not yet completely opened up, and an actual advance of the red cells towards the ovum.

I have pointed out in previous paragraphs that the fluid and blood escape from the vessels in the menstruating mucosa, in which the changes are similar to those present here, is due to an active tissue imbibition due to protoplasmic alterations that lead to the production of diffusion streams radiating from the vessel lumina. I have also pointed out that the uterine mucosa is especially fitted for the occurrence of this with the greatest possible efficiency. The same tissue changes I have shown to be induced by the chorionic influence (enzymes) in the pregnant tube, in the uterine muscular coat and mucosa in the case of retained placental fragments, and in the uterus in chorion-epithelioma. These facts taken in consort would suggest that in the mucosa of the pregnant uterus exactly the same factors are operating.

In addition to this evidence, which, though strong, is of a circumstantial nature, a study of the minute microscopic details reveals direct and indisputable confirmation of the ideas I have advanced.

In/

In the first place throughout the mucosa in my specimen there is seen to be an appearance of the very intricate tissue network, the function of which I have fully discussed in connection with the menstruating state. On preceding pages I have adduced evidence in support of the belief that this structure is to be taken as an evidence of an active diffusion into, and imbibition of fluid by, the stroma protoplasm, which determines not only the oedematous but also the blood escape. (Plates III, IV, and V. and Section II.). In the vessel walls, also, in the specimen under discussion, it is often possible to recognise the same evidence of an active fluid imbibition as I have described in connection with the menstrual changes (Plate XIX). For a full discussion of this subject I would refer the reader to the corresponding section of this research. (Section II).

This specimen of a very early human ovum is thus seen to furnish complete confirmation of the views I have advanced regarding the peculiar structure of the mucous membrane and its probable bearing on the changes present in pregnancy, and it establishes the completeness of the analogies which I was led to trace between the activities of the chorionic cells in abnormal sites and in the normal state.

In/

In concluding this discussion on the vascular changes I may state that I feel convinced that to explain fully the mode in which the trophoblastic surface is flushed with the maternal blood we have to recognise the importance of the active absorption of the blood fluid by the rapidly enlarging ovum. This specimen would seem to confirm this in the fact that the red cells are actively streaming into the implantation chamber from all sides. The cavity is densely packed with the red corpuscles, suggesting that the fluid is being absorbed as quickly as it enters, in this way establishing a constant flowing of the blood towards the place where it is needed.

The haemorrhagic infiltration of the tissues in this case, though similar in its location to that normally present as proved by a study of all the recorded very early ova, would seem to be greater in quantity than that ordinarily found. This subject I have not had the time to enter into fully. The appearance, however, would seem to warrant the conclusion that it is the agent which determined the occurrence of the abortion. The necrotic layer of the decidua immediately bordering on the gestation cavity would seem to be due to a degenerative change in the newly formed decidual tissue - in it decidual cells in varying stages of disintegration are present.

The vascular and tissue changes just described/

described prove conclusively that there is acting some extracellular influence emanating from the developing ovum, which tends to lead to an active tissue imbibition by the maternal tissue of the blood fluid, and corpuscles. This is most evident in the immediate proximity of the ovum, but it extends for a considerable distance into the adjoining tissues. In view of these facts and the observations recorded on previous pages it seems to me that the justice of the conclusions I have formulated with regard to the function of the decidual membrane is firmly established. The decidual enlargement and packing together of the stroma cells must be for the purpose of preventing the uncontrolled ploughing-up of the maternal tissues by the fluid and blood which would otherwise inevitably occur throughout the entire mucosa as the chorionic influence gradually extended the sphere of its activity. Before the complete development of the decidual change the blood and fluid are not even efficiently localised to the region where they are needed. This is well brought out by comparing this specimen and that of Peters with the conditions present where there is a better developed decidual membrane.

DESCRIPTION/

DESCRIPTION OF THE OVUM AND THE IMPLANTATION CHAMBER.

Like that present in other early ova the cavity is drawn out parallel to the surface of the mucosa. Its measurements are, so far as the specimen permits of their being taken,

Maximum Length = 1.5 m.m.

" Breadth = .97 m.m.

In shape it is almost a perfect oval (Figure 193). In a section cut across the decidual lobule towards its broader and longer aspect i.e. base, the ovum is seen lying in the cavity, for the most part, unattached. It consists of a blastocyst, the cavity of which is occupied by a number of branching mesenchyme cells, in the interstices between which is present a granular sort of material, suggesting a coagulum. At no part was there any evidence of an embryonic rudiment. The surface of the blastocyst is very irregular in nature, being thrown into numerous depressions and elevations, the latter apparently corresponding to rudimentary villi. The chorionic epithelium consists of a typical Langhans' layer covered, in places, by a multinucleated plasmodium or syncytium. In places the cellular covering consists/

consists of one layer of cells, in other places, especially at the tips of the villous projections, it is heaped up to form several layers. In some few places isolated syncytial buds or the extremity of one of the projections is seen lying up against the necrotic zone of the decidua. Scattered about the implantation cavity chorionic cells, singly or in groups, are seen. In some places there is present a number of large mononucleated cells, which Teacher and Bryce, Graf v. Spee and others have described. These are probably foetal in origin.

At the region of the base of the lobule
the measurements of the ovum are

Length of Blastocyst = 1.125 m.m.

Breadth " " (at widest) = .67 m.m.

" " " (at narrowest) = .075 m.m.

As already mentioned a part of the ovum is wanting and it is therefore impossible to give the other dimension. It would seem not unlikely that the first measurement given above indicates the longest diameter of the blastocyst and in proof of this I would advance the following considerations. In all the early ova recorded the longest diameter is parallel to the surface of the decidua and as the sections in this case have been carried across the decidual lobe/

lobe approximately parallel to the mucosa surface it seems certain that some of the sections cut the ovum across in its longest diameter. The fact that the sections were thus made, and not at an angle to the decidual surface, is proved by the descriptions of the successive sections, which I have given. As the sections which were rescued are traced in series it is found that the breadth of the blastocyst gradually increases to a maximum and then gradually diminishes until it ultimately disappears. We thus see that in the portion of the ovum recovered we have the greatest diameter in one direction. This is about .7 m.m. The length of the blastocyst in the section corresponding to this maximum breadth is appreciably smaller than that given above (1.125 m.m.). This would seem to indicate that the ovum has been cut across somewhat diagonally. These considerations, in any case, demonstrate with a distinct measure of certainty that in the specimen we are dealing with one of the earliest ova ever discovered. In this place I do not intend to enter into an analytical comparison of it with other early ova. This I shall have to postpone till I have had a fuller opportunity of studying it more carefully. (In this place I may state that Dr. Teacher of Glasgow to whom I have shown the specimen, /

specimen, and to whom I am indebted for valuable suggestions regarding its probable relative position with regard to other early specimens, agrees in thinking that in the sections the largest diameters are represented).

In figure 193 it will be seen that the blastocyst tapers somewhat towards the free aspect of the decidual lobule. As the sections are pursued it is found that this portion of the ovum comes progressively nearer and nearer the wall of the implantation chamber, until it ultimately comes to project on the free surface of the mucosa. (Figures 197-201). On either side the walls of the chamber are seen to become markedly thinned out over the rounded aspect of the exposed blastocyst until they completely disappear. Here the blastocyst, denuded of its epithelial surface, is in direct relation to the uterine cavity. The edges of the rounded orifice in the decidual wall through which the ovum is projecting are seen in Figure 199. The appearances described constitute a very remarkable condition, which is amenable to one or other of two explanations. (1) It indicates an attempt on the part of the imbedded ovum to extrude itself by destroying the roof of/
of/

of the enclosing cavity wall, or (2) it furnishes a demonstration of the manner in which the ovum becomes implanted and ultimately reaches its bed in the deeper subepithelial portions of the mucous membrane. In the latter case the exposed region would correspond to the oldest part of the ovum, the deeper part to that portion which is developing in the direction from which the nourishing blood is being derived, somewhat in the fashion in which a villous or a chorion-epitheliomatous mass grows through a vessel wall and thereafter develops in a luxuriating manner in the vessel lumen.

This question, with, in addition, the light which the specimen sheds on the manner in which the implantation chamber is formed, and, also, the absence of the embryonic rudiment, I shall leave over till a future occasion.

ADDITIONAL/

ADDITIONAL CONFIRMATORY EVIDENCE DERIVED
FROM A SECOND EARLY OVUM SOMEWHAT
OLDER THAN THE LAST.

For the opportunity of examining this specimen I am indebted to the kindness of Dr. J. H. Teacher. He has placed the whole specimen, consisting of 1050 serial sections, at my disposal for the purpose of completing the evidence in support of the contentions advanced in the preceding pages of this research. The case is as yet unpublished.

The specimen consists of a complete ovum imbedded in the decidua, which was obtained by abortion. The maximum measurement (which, as in all other early ova, corresponds to the plane parallel to the surface of the mucosa) is 5.5 m.m. The maximum breadth (i.e. depth from surface inwards) is 2 m.m. If we are to adopt the conclusions of Teacher and Bryce regarding the age of young ova in terms of their size this specimen will correspond to an age of about 17-18 days.

The blastocyst is almost perfectly oval on section and is lying, for the most part, unattached in the implantation chamber. All round its circumference/

circumference the surface of the blastocyst is separated from the wall of the enclosing cavity by only a small interval, in which a large number of well-formed villi are present. In a few places these are found to be incorporated at their tips with the maternal tissues. The cavity of the blastocyst is, as in the last specimen, occupied by a number of freely branching mesenchyme cells, separated by a granular-looking substance. In sections towards the equator the centre of the blastocyst is seen to be formed by a clear space, apparently due in part to a shrinkage of the contained mesenchyme. There is no evidence of an embryonic rudiment.

The epithelium of the blastocyst surface and of the villi is composed of the ordinary two layers - the Langhans' cells and the syncytium. The former are in most places several layers thick. In many places isolated trophoblastic cells and syncytial buds are found lying apparently free in the implantation cavity.

DESCRIPTION OF THE DECIDUA AND THE DECIDUAL VESSELS.

In the immediate proximity of the ovum chamber there is present a zone of necrotic tissue, similar/

similar in every respect to that exhibited by the last specimen. Outside this the mucosa has been almost completely transformed into a decidual membrane, identical with that characteristic of the later periods of pregnancy. In this respect this ovum differs from the last specimen, in which the decidual change was limited to the immediate proximity of the ovum.

Scattered throughout the decidua there are numerous areas of haemorrhagic escape.. In the proximity of the gestation cavity this condition is present to an excessive degree. The blood cells are seen streaming through the vessel walls into the surrounding tissues and across the tissue intervening between the affected vessels and the implantation chamber. Into this the blood can be seen flowing in large quantity through the necrotic zone of the decidua. The manner in which the blood is leaking from the vessels is identical in every respect with that present in the last specimen, and it, therefore, coincides with the mode in which the mucous membrane becomes suffused with blood during the menstrual process, (Figures 202-203). Although the actual nature of the vascular changes is similar to that occurring in menstruation the degree in which it has taken place in this case is considerably in/

indicates that in it we must recognise the manner in which the maternal vessels open during pregnancy.

As I have said the bleeding, whilst most marked in the proximity of the ovum, is evident at a considerable distance, in this way coinciding with the appearances presented by the last specimen and those exhibited by the maternal tissues in the abnormal sites of chorionic activity which we have studied (pregnant tube, retained placental fragments, and chorion-epithelioma). In the last section I noted that in the mucosa there was distinct evidence of an active fluid imbibition on the part of the tissues like that present in the abnormal regions of foetal invasion. In this specimen the same evidence is easily obtained and is, for the most part, clearest in the decidua at some little distance from the ovum. The changes are even more convincingly demonstrated than in the last specimen. The rationale of this is not difficult to understand, when it is remembered that in the menstrual mucosa, in the pregnant tube etc. it was found that the greater the support of the vessel wall the clearer the evidence of the active fluid imbibition by the component cellular elements. The same is true here, but in this case the support is furnished by the well-marked decidual/

decidual change in the stroma cells. On Plate XX. are represented the appearances typically present, appearances which do not require more than a short description in view of the preceding investigations. There is the same fluid imbibition by the lining cells, and by the cells of the vessel wall. In Plate XX, . the active tissue change is actually seen to be dragging the red cells from the vessel lumen.

The fact that the decidual change in the stroma elements has forced the process into prominence would seem to indicate that it is specially intended for the purpose of resisting the oedematous and blood escape which otherwise would inevitably lead to an irregular and uncontrolled tearing up of the entire mucous membrane.

SUMMARY./

S U M M A R Y.

- (1) From a study of two very early ova imbedded in the decidua I have been able to obtain direct confirmatory evidence in favour of the contentions advanced on the preceding pages regarding the mode of action of the chorionic epithelium.
- (2) The oedematous and blood escape are dependent on tissue changes associated with an active imbibition. These are most evident in the immediate proximity of the engrafted ovum but they are found at a considerable distance. The fact that these changes are detected in the decidual membrane no matter how the specimens are obtained (I have previously described them in pregnant uteri removed entire by operation) disproves, what otherwise might be urged, that they are abnormal and are simply to be looked on as the agents responsible for the abortion in the two early ova.
- (3) The Decidual Enlargement of the stroma cells must be for the purpose of localising the blood/

blood escape to the regions where it is required. It prevents, after it is well developed, an irregular and excessive ploughing-up of the mucous membrane which would otherwise certainly occur.

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